PROSPECTIVE ANALYSIS OF VOIDED AND BARBOTAGE URINE CYTOLOGY IN THE ROUTINE FOLLOW UP OF NON-MUSCLE INVASIVE TRANSITIONAL CELL CARCINOMA OF BLADDER

DISSERTATION

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CERTIFICATE

This to certify that the work incorporated in this dissertation entitled **"PROSPECTIVE ANALYSIS OF VOIDED AND BARBOTAGE URINE CYTOLOGY IN THE ROUTINE FOLLOW UP OF NON-MUSCLE INVASIVE TRANSITIONAL CELL CARCINOMA OF BLADDER"** is a bonafide work done by **Dr. Srinivas** in partial fulfillment of the rules and regulations of MCh Branch IV (Genitourinary Surgery) examination of the Tamil Nadu Dr. M. G. R Medical University Chennai to be held in August 2011.

Guide

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CONTENTS

INTRODUCTION

Bladder cancer is one of the commonest malignancies in humans, with an estimated 200,000 new cases per annum world wide[1].It is two and half times commoner in males than females[2]. Its incidence, like most other malignancies, increases with age, though it can occur in any age[3]. Several important risk factors have been identified for bladder cancer including cigarette smoking, exposure to chemicals such as aniline dyes, benzidine compounds, aromatic amines; "slow acetylators" metabolic phenotypes and the presence of chronic inflammation or infection of the bladder[4]. Histologically, greater than 90% of bladder cancers are transitional cell carcinomas; squamous cell cancers and adenocarcinomas constituting 5% to 6% and 1% respectively[4]. Around 70% of all transitional cell carcinomas are classified as superficial lesions i.e., they do not invade more extensively than into the lamina propria. They comprise of a heterogeneous group ranging in both histologic grade (low or high) and stage T_a confined to the mucosa, T_1 invasive into the lamina propria, or CIS - carcinoma in situ [5]. Even with early adequate treatment there is an overwhelming propensity of carcinoma bladder to recur. Up to 70% of superficial tumours recur within 5 years, a figure that rises to 90% in 15 years. Over 20% of the superficial tumours progress to invasive disease with a poor prognosis[6-7]. This entails an intensive follow up protocol to detect recurrences at the earliest. Presently cystoscopy remains the primary diagnostic modality to detect carcinoma bladder.

Cystoscopy has a reported sensitivity of over 90%[8] to detect tumour recurrence. It however is invasive, uncomfortable and expensive, apart from the

loss of man hours at work and the requirement for a trained urologist. Moreover, the classic recommendation for cystoscopic surveillance in bladder cancer has been, once every 3 months for first year, every 6 months for the second year, and yearly thereafter. These are authority based opinions with little empirical backing. Such schedules may be inadequate for high risk patients and overzealous for individuals with solitary, low grade, low stage lesions[9]. It is also limited by low specificity and positive predictive value when used to evaluate lesions occurring in the bladder during the follow up of patients with TCC bladder.[8]

To detect carcinoma of the urinary bladder noninvasively at initial presentation, or at follow up cytological assessment remains the standard assay[10]. It is however plagued by low sensitivity, on an average less than 50%; and as low as 30% in low grade, low stage disease[8]. It is a laboratory based investigation, cumbersome and expensive, requiring trained personnel for its interpretation, with slow sample collection and minimal potential for automation. Bladder cancer is a chronic illness with no definite and suitable curative measures. The main goal in their management is to diagnose the primary and recurrent tumour as early as possible, while it is amenable to local resection.

Urine Cytology

Urinary cytology is the study of cells from the bladder and the upper urinary traact. Bladder cells are obtained from voided urine or from lavage fluid. Usually, three specimens are acquired for analysis. Urine cytology is especially useful in diagnosing transitional carcinoma in situ (TIS) and high-grade transitional cell carcinoma (TCC). In fact, urine cytology is positive in roughly

95% of patients with high-grade tumors. Unfortunately, urine cytology does not detect low-grade lesions very well, since cellular changes often are very subtle in early malignancy; only about one-third of all cytologic findings for low-grade lesions are positive. Urine cytology features that suggest cancer include[13]:

- Increased nuclear to cytoplasmic ratio
- Irregular nuclear border
- Hyperchromasia
- Irregular clumping of chromatin
- Abnormal location of the nucleus (cell center)
- No cytoplasmic vacuolization (spaces within the cell fluid)

In addition, small percentages (1% to 12%) of cytology findings are "false positive". False-positive cytologic results may be caused by factors such as inflammation or changes brought on by radiation therapy or chemotherapy[11-20].

Urine cytology complements cystoscopy by offering high sensitivity for the detection of high-grade TCC. However, the accuracy of urine cytology appears to be associated with considerable variability. Positive results are obtained in 31–72% of patients with bladder cancer, when all tumour grades and stages are considered[11–20]. The sensitivity is highly dependent on tumour grade [7, 9, 10]. Low-grade tumours are not reliably detected by cytology, whereas high grade tumours are detected 79% of the time [7, 9, 10]. Variations in the histological criteria of

malignancy in bladder tumours, differences in the preparation techniques of smears, suboptimal specimen quality and differences in pathologists expertise with the test have been offered as possible explanations [17]. These difficulties are compounded by artefactual changes that may be introduced by infection, catheterization, electro cauterization, bladder washing, previous intravesical therapy or previous radiotherapy [18]. These variables affect the urothelium and may undermine the sensitivity of cytology [18]. For example, Wiener et al. [18] reported 71.4% accuracy in newly diagnosed tumours versus 44–50% after transurethral resection, radiotherapy or intravesical therapy.

Therefore many variables might decrease the ideal performance characteristics of urinary cytology; thus we explored the ability of urinary cytology to predict an established recurrence of previously known non muscle invasive

TCC and to objectively evaluate the difference in cytologic findings between specimens of voided and barbotage sample of urine.

This study is an attempt to review the practice of urine cytology examination in our setting of nonavailability of trained cytopathologist at all point of time and also to assess whether a barbotage sample of urine gives a better yield for diagnosis of nonmuscle invasive TCC bladder during the follow up.

REVIEW OF LITERATURE

Urine Cytology:

The microscopic evaluation of urinary sediment dates back to the 19th century when Sanders[48] and Dickenson[49] described the presence of abnormal cellular findings in the urinary sediment of men who were subsequently diagnosed with bladder cancer. However, it was not until the mid-20th century that modern urine cytology was introduced by Papanicolaou and Marshall [54] and more formally applied in the clinical detection of bladder cancer. During the past 20 years, the use and utility of urine cytology in the diagnosis and management of urothelial carcinomas has become commonplace and, in some instances, a standard of practice. Since the first satisfactory technique for demonstrating cancer cells in centrifuged urine was described by Papanicolaou and Marshall in 1945, urine cytology has been an integral part of cancer screening. Several requirements must be met for urinary tract tumours to be detected by cytology. Since it is based on the evaluation of morphological variables of the exfoliated cells, there must be contact between the lesion and urine, the lesion must regularly shed cells and these cells must be sufficiently different from normal cells to be identified[14]. Important intrinsic tumour factors that affect cytology include tumour grade, configuration (multicentricity, stage) and location (upper or lower tract). Interpretation of the urine specimen can be challenging, especially when urolithiasis and instrumentation are factors and it is observer dependent[15]. The analysis is most successful when the sample is immediately transported to the cytology laboratory for preparation. Improper handling and delay in transfer may result in the destruction or degradation of cells.

Application and collection of urine cytology by urinary tract site[50]

Site	Specimen	Comment
Bladder Screening for high-risk patients (hematuria, carcinogen exposure, irritative symptoms)	Voided	Late morning void preferred
Diagnosis of primary malignancy and precursor Lesions	Catheterization/ endoscopy	Avoids skin/urethral contamination
Diagnosis of secondary malignancy (metastases, direct extension, fistulization)	Wash/barbotage	Specific to bladder,increased diagnostic yield
Surveillance after therapy for primary tumor (surgery, immunotherapy, chemotherapy) Surveillance after therapy for upper tract tumor		
Urethra Surveillance of urethral remnant after cystectomy	Voided Wash	Surveillance after cystectomy/orthotopic Neobladder Surveillance after cystectomy/cutaneous diversion/urethral remnant
Renal pelvis/ureter Screening for high-risk patients	Voided	Nonspecific, low yield
Diagnosis of primary malignancy and precursor lesions	Catheterization	Specific to side and level in urinary tract
Surveillance after therapy for primary upper tract lesion (eg, after endoscopic therapy)	Wash	Increases diagnostic yield
Surveillance of upper tract after cystectomy	Brushings	Direct exfoliation of suspicious area

While cytology has a reported specificity of greater than 93%, its sensitivity is only 25-50%, particularly for the detection of low grade and low stage tumours. However, this sensitivity increases considerably in detecting carcinoma in situ (CIS) and high grade and high stage transitional cells carcinomas and it is in this group of patients that it proves particularly useful. The poor accuracy in the detection of low grade, low stage tumours confines it to use as an adjunct alongwith cystoscopy in diagnosing bladder cancer[10].

Diagnostic yield of urine cytology in malignancy [50]

	True-Positive Cytologic Findings (%)*	
Tumor Grade	**Voided [51,52]**	**Bladder Wash [53]**
1	17	70
2	72	98
3	94	100
CIS	100	100

* “Suspicious” and “positive” diagnoses but not “dysplasia.”

Urine cytology is undeniably inadequate and is plagued by low sensitivity and subjective diagnostic criteria for the majority of lesions. Additionally, duplication of the three-tiered grading system is difficult cytologically.

CYTOLOGY OF NONMUSCLE INVASIVE BLADDER CANCER

In patients who are screened for bladder cancer, the overall sensitivity of positive urine cytology is approximately 40% to 6O%." [(21, 30)] A positive cytologic diagnosis is highly predictive of TCC, even in the presence of normal cystoscopy.[24] Malignant cells may appear in the urine long before any

cystoscopically detectable lesion emerges, [26] leading to a seemingly inflated rate of false-positive results. One variable affecting the sensitivity of urine cytology is the type of specimen.

Voided urine specimens are generally hypocellular and degenerated. They may also contain significant amounts of skin and vaginal contamination, particularly when collected from female patients. The sensitivity is augmented when three specimens are obtained on three separate days. For one, two, and three voided urine specimens, sensitivities of 41%, 41% and 60% have been reported, respectively.[26]

Catheterized urine and bladder washes have higher cellularity and less contamination but require an invasive procedure that may introduce instrumentation artifact.[25]

All urine cytology specimens are sufficiently dilute as to require some form of cell concentration. Initially, cytologic findings were assessed on smears made from the sediment of centrifuged specimens[27]. Subsequently developed methods include thin membrane filtration, cytocentrifugation, and, most recently, monolayer technology. Malignant cells identified in cytologic specimens may come from either low-grade or high-grade lesions. Cells designated as low grade should correlate with histologic grade I lesions and some histologic grade TI lesions. Cells designated as high-grade correlate with some grade 2 lesions and all grade 3 lesions but also with TCC in situ.[26]

High-grade Transitional Cell Carcinoma and Transitional Cell Carcinoma In Situ

Urine cytology has excellent performance statistics in patients with high-grade lesions, which is the primary reason for its continued efficacy as a screening and surveillance device. The sensitivity is at least 90%, and the specificity reaches 98% to 100%.[22,26] The cytomorphologic features are well-characterized and easily recognized, leading to cytologic designations of “positive for malignant cells” in most cases and ”suspicious for malignancy” in some. Tumor cells are larger than normal with increased nuclear-to-cytoplasmic (N / C) ratios and eccentrically placed nuclei. Pleomorphism is evident, and individual nuclei have irregular membranes and often prominent nucleoli. Marked nuclear hyperchromasia is present, as well as coarse irregularly distributed chromatin, frequent mitotic figures, and vacuolated amphophilic cytoplasm[22, 26]

Low-grade Transitional Cell Carcinoma and Dysplasia

The overall low sensitivity of urine cytology is explained almost exclusively by its unreliable detection of well-differentiated, low grade lesions. Because the cells of such tumors so closely resemble normal urothelium, cytopathologists opt for terminology such as ”atypical urothelial cells present; cannot rule out a low-grade lesion.” Much effort has focused on identifying features to aid in the distinction between normal urothelial cells and well-differentiated malignant cells.

According to the review of the literature by Renshaw and co-workers in ‘The cytology of low-grade urothelial neoplasm’s’, this review has showed

sensitivities ranging from 0% to 100% and specificities ranging from 6% to 100%.[31]

D eMay[22] mentions the presence of varying numbers of single small "coy cells" in the background that have very high N/C ratios and abnormal slightly hyper chromatic nuclei with slightly coarse chromatin and irregular nuclear membranes. Using stepwise logistic regression analysis Raab and co-workers[28] identified the three criteria most useful in discriminating low-grade TCC from nonneoplastic processes :

1) cytoplasmic homogeneity, defined as the absence of cytoplasmic vacuoles;

2) an increased N/C ratio, defined as greater than 1 to 3; and

3) irregular nuclear borders.

When at least two of the three criteria were present, the sensitivity was 85% and the specificity 96% when applied retrospectively.[28]

INCREASING THE SENSITIVITY OF CYTOLOGY

Perhaps the greatest determinant of the sensitivity of urine cytology is the level of Cytopathologist expertise. Nevertheless, much effort has focused on developing ancillary techniques to improve the sensitivity of urine cytology. Of the large variety of methods tested, techniques for detecting nuclear aneuploidy, the presence of cell markers such as Lewis X antigen, and over expression of p53 seem most promising.[30]

A review of urine cytology in the diagnosis and follow up of bladder cancer at Roswell Park Memorial Institute from 1971 to 1981 was reported by Zein TA et al. All patients had biopsy-proven transitional cell carcinoma of the bladder. A total of 677 patients underwent 2,877 cytological evaluations. Of these, 317 patients had concomitant cystoscopy, cytologic evaluations and bladder biopsies. A total of 1,091 evaluations were performed in this group. The overall incidence of positive cytology in the presence of biopsy-proven baldder tumor (all grades included) was 74.4%[32]. A linear correlation is present with grade, stage and positive cytology; high-grade tumors and carcinoma-insitu showed 89.9% and 96.9% incidence of positive cytology, respectively. Grade II tumors showed a 64% incidence of positive cytologies. Regarding correlation with the pathological stage, submucosal involvement of the urothelium was associated with a 62% incidence of positive exfoliative urine cytology, while 80% of tumors invading the bladder muscle were found to have a positive cytology[32].

Mungan NA et al from the Department of Urology, Numune Hospital, Ankara, Turkey did a study to assess the sensitivity of urine cytology by using different portions of voided urine cytology (VUC) and bladder wash material cytology (BWC).

52 patients with biopsy-proven superficial transitional cell carcinoma (TCC) the bladder were studied. Voided urine specimens were divided into a first stream, mid-stream and terminal stream. Bladder wash material was also divided into a first portion, mid-portion and last portion. All portions were investigated for cytology abnormalities.

Sensitivity for the detection of malignant cells was 34.6, 38.5 and 38.5% for the first, mid- and terminal stream of VUC and 34.6, 38.5 and 34.6% for the first, mid- and last portion of BWC, respectively. The sensitivity of VUC was 20-25% for grade I, 30-40% for grade II, and 50-75% for grade III tumors, respectively. The sensitivity of BWC was 25% for grade I, 35-45% for grade II, and 33-50% for grade III tumors, respectively. There was no statistical significant difference for sensitivities between either grades ($p = 0.06$) or portions or streams ($p = 0.3$) of VUC and BWC[33].

Robert S et al from University of Texas Southwestern Medical Centre, Dallas, Texas conducted a retrospective study to evaluate the accuracy of cystoscopy and cytology in predicting the histopathologic features of suspicious cystoscopic lesions. They reviewed the bladder biopsy records and cytology at two institutions from July 2001 to July 2004. Intraoperative biopsies were performed for positive (papillary or sessile) ($n = 155$) and equivocal ($n = 101$) lesions found during office cystoscopy. For patients without a history of TCC, cytology had a sensitivity and specificity of 66.7% and 100%, respectively. The PPV of cytology in identifying cancer at biopsy was 100% (30 of 30). In contrast, cytology was falsely negative in 15 (63%) of 19 patients. The sensitivity, specificity, NPV, and PPV for cytology in patients with a history of TCC was 63.2%, 70%, 22%, and 92.3%, respectively. For all patients with positive lesions, false-negative cytology findings were identified in 36 patients. Of these 36, 27 (75%) had low-grade tumors at biopsy and 9 (25%) had high-grade tumors at biopsy. Those lesions with atypical cytology had normal pathologic findings in 3 (21%) of 14 of those with a history of TCC and in 0 of 8 of those without a history of TCC[34.]

Planz B et al from Golzheim Paracelsus clinic, Friedrich-lau-Str. Duesseldorf, Germany prospectively studied the value of urine cytology in the diagnosis of bladder cancer. One thousand three hundred and eighty voided urine and bladder wash specimens of 495 patients were evaluated by urine cytology. In this study urine cytology revealed a sensitivity of 38% and a specificity of 98.3% with a positive and negative predictive value of 90.6% and 78.6% respectively. Sensitivity increased significantly with malignancy grade. In high grade tumors sensitivity improved from initial 52.2% to 78.3%.In sensitivity and specificity of voided and barbotage washing samples no significant difference was detected.

Renshaw AA et al from Brigham and Women's Hospital, Boston, Massachusetts, USA in there study on urine cytology in grade 1 TCC, the sensitivity ranged from 22 to 44% and specificity from 69% to 85% and positive predictive values from 59% to 66%[31]

Karakiewicz PI, et al from Department of Urology, University of Montreal, Montreal, Quebec, Canada did a retrospective study to assess the contemporary inter-institutional accuracy of urinary cytology in predicting the recurrence of transitional cell carcinoma (TCC) of the bladder, in a large multi-institutional cohort from four continents. Ten institutions contributed 2542 patients with a history of superficial TCC, of whom 898 had TCC recurrence. Age- and gender-adjusted logistic regression models were used to evaluate the association between urinary cytology and TCC recurrence. Cytology was positive in 19 (10-38)% of patients; recurrence was identified in 35 (27-54)% of patients[35]. The sensitivity was 38-65% across institutions. Urinary cytology varied significantly in

its ability to predict recurrence of bladder cancer. Institution-specific predictive accuracy adjusted for gender and age was 0.627-0.893. Stratifying by grade and stage only partly attenuated the discrepancies between centre's[35].

Loh CS et al from Department of Urology and histopathology, Broadgreen Hospital NHS trust, UK did a prospective study to evaluate the value of exfoliative urine cytology in predicting recurrent tumour in patients undergoing surveillance for TCC. The study comprised 111 patients (85 men and 26 women) with an established histological diagnosis of TCC of the urinary bladder who were assessed over an 8-month period. Each patient was asked to submit a specimen of early-morning urine and freshly voided urine 2 weeks before the planned review cystoscopy. From 111 patients, 118 assessments met the full criteria for inclusion in the study. Malignant cells were reported in one or both of the paired urine specimens in 29 cases, being positive in both the early morning urine and freshly voided urine specimens in 24 of these. Typical cells were found in one or both specimens in 34 cases, being present in both the early morning urine and freshly voided urine specimens in 24 instances; 38 paired specimens were considered to show normal cytology, a further five were normal in one specimen only, and in 12 cases both the early morning urine and freshly voided urine specimens were considered undiagnostic[36].

Of the 118 cystoscopies, 56 revealed abnormal mucosa, the biopsies of which were neoplastic in 39 specimens, with TCC in 34, moderate epithelial dysplasia in three, mild dysplasia in one and adenocarcinoma of prostate in one. The other 17 biopsies revealed radiation changes in four, chemotherapy changes

in two, chronic inflammation in eight, an inadequate biopsy specimen in one and no significant histological abnormalities in two.

The outcome after cystoscopy and biopsy in cytologically positive and negative patients is shown in tables 1 and 2, respectively.

Urine cytology positive

	Malignant cells (n [%])	**Atypical cells (n [%])**	**Total (n [%])**
Normal cystoscopy	7(11)	17(27)	24(38)
Recurrent TCC	17(27)	10(16)	27(43)
Dysplasia	1(2)	3(5)	4(6)
Prostate adenocarcinoma	1(2)	0	1(2)
Chemotherapy changes	2(3)	0(0)	2(3)
RT changes	0(0)	2(3)	2(3)
Inflammation	1(2)	2(3)	3(5)
Total	29(46)	34(54)	63(100)

Urine cytology negative

	Normal cells (n [%])	**Non-diagnostic cells (n [%])**	**Total (n [%])**
Normal cystoscopy	29(53)	9(26)	38(69)
Recurrent TCC	5(9)	2(4)	7(13)
RT changes	2(4)	0(0)	2(4)
Inflammation	5(9)	0(0)	5(9)
Normal biopsy	1(2)	1(2)	2(4)
Biopsy undiagnostic	1(2)	0(0)	1(2)
Total	43(78)	12(220)	55(100)

Of the 29 instances where malignant cells were present in one or both of the paired urine specimens, 22 had abnormalities at cystoscopy. Seven patients with malignant cytology had no mucosal abnormality at cystoscopy. One was later found to have prostatic adenocarcinoma, one had a bladder calculus and two were thought on subsequent review to have had normal cytology, degenerate urothelial cells being mistaken for malignant cells.

Of the 34 cases with atypical cells in one or both of the paired urine specimens, 17 had abnormalities at cystoscopy. The other 17 cases with atypical cells at cytology showed no abnormality on cystoscopy.

In 43 cases with normal cytology, cystoscopic abnormalities were preset 14 cases; there were 12 cases in which both the urine specimens were deemed undiagnostic on cytology.

The sensitivity of urine cytology in identifying all tumours and dysplasia was 32/39 (82%) with a specificity of 32/63 (51%). Table 3 shows the sensitivity of urine cytology compared with the histopathological stage and grade of the all the recurrent TCC . In this small group of patients, the sensitivity was higher in high grade (G2/G3) TCC.

Urine cytology results for the histological grades/stages of recurrent TCC

Grade/stage	number	Positive cytology	Sensitivity (%)
G1/pTa	10	6	60%
G2/pTa	10	8	80%
G2/pT1	4	4	100
G3/pT1	3	2	67
G3pT3	1	1	100
G3/pTis	6	6	100
Total	34	27	79

This study has shown a high rate of detection of recurrent TCC using exfoliative urine cytology which was more pronounced with tumors' of higher grade and stage compared with those of lower grade. All the patients with dysplasia had abnormal cytology. On the other hand there was a high level of false positive results, with 24 of 63 having normal mucosa at cystoscopy and 31 of 63 being normal or having non-neoplastic abnormalities.

Tawfik Zein et al[37], from Department of Urologic Oncology and Pathology, Roswell Park Memorial Institute, Buffalo, New York, did a prospective study of 136 patients with biopsy proven bladder tumor who underwent 311 evaluations with cystoscopy, urinary cytology, bladder washing and, bladder biopsies.

Of the 136 patients 89 had bladder biopsies positive for transitional cell carcinoma at the time of the study and were evaluated for comparison of urinary cytology and bladder washing. The remaining patients had a history of bladder

tumour and were followed for recurrent disease. Urinary cytology and bladder washing specimens were positive in 71 and88 per cent of the cases, respectively.

Concomitant urine and bladder washing specimens were available in 73 patients with Histologically proved TCC and the results were compared according to tumour grade.(table 1). Cytology studies also were obtained in 54 patients in whom bladder mucosal biopsies showed dysplasia only without evidence of tumour. Of these 54 patients 33 had concomitant bladder washing and urinary cytology studies, including 30 with moderate dysplasia pathologically who also were evaluated cytologically. The results in the latter 30 patients showed a significant increase of abnormal cells in the bladder washing specimens(9 patients, 30 per cent) compared to those obtained by urinary cytology(5 patients, 16.6 per cent). There was a 23 per cent incidence of random biopsies positive for carcinoma in situ. Of these patients 10 had a high grade primary tumour and multiple biopsies were positive in 55 per cent , while 9 with a low grade primary tumour had a 10 per cent evidence of carcinoma in situ.

The superiority of the bladder washing over urinary cytology might be attributed to,

1. Better preservation of cells,[43]
2. Less contamination in the background,[38]
3. Better preservation of the bladder epithelium,[38]
4. More details of nucleus and cytoplasm,[43]
5. Immediate fixation,[44]

Table 1 Bladder tumour according to grade and cytological correlation with negative, positive and suspicious interpretations [37]

Urine cytology (%)					Bladder washing (%)		
					positive	negative	suspicious
Grade	**No.tumors**	**positive**	**negative**	**suspicious**			
1	16	25	50	25	31	37	22
2	21	57	4	39	85	4	11
3	23	74	0	26	87	0	13
Ca in situ	13	77	15	8	85	7	8

Table 2 Comparison of urine cytology and bladder washing results according to grade.

References	No. of Pts	Grade	% pos.cytology	% pos.bladder washings
Harris et al (38)	20	2	40	80
		3	60	100
Eposti et al (39)	195	1	-	28
		2	-	76
		3	-	89
National bladder cancer Collaboration Group A(40)	114	1	13	40
		2	39	35
		3	77	88
MacFarlane, Ceelen, Taylor et al (41)	119	Low	55	-
		High	88	-
Dubernard, Devonec, Amiel, Bouvier et al (42)	51	1	9	-
		2	75	-
		3	93	-
Tawfik Zein et al (37)	73	1	25	31
		2	57	85
		3	74	87

These studies demonstrate the superiority of bladder washings over urinary cytology in detecting abnormal cells and malignant cells in patient with TCC bladder.

NEW HORIZONS IN URINARY TESTS FOR UROTHELIAL CARCINOMA

FLOW CYTOMETRY

Voided urine cytology does not contain enough cellular content; therefore, flow cytometry uses specimens obtained by bladder wash through a catheter or cystoscope. Flow cytometry seeks to detect aneuploid cells as a marker of underlying malignancy.[55] Recent studies comparing flow cytometry with conventional urine cytology have demonstrated perhaps only a marginally increased sensitivity, but significantly lower specificity.[56,57]

Ancillary techniques to improve the sensitivity of urine cytology have been insufficiently additive to have much clinical value. Several promising bladder tumor markers have been investigated as potential screening tools and are summarized in Table 3**.** BTA, nuclear matrix proteins, and fibrin / fibrinogen degradation products share lower specificities han urine cytology and may have high rates of false positivity. Telomerase is highly sensitive and highly specific but is not readily available as a point-of-service test. Hyaluronidase and hyaluronic acid are promising prognostic markers, but hyaluronidase does not detect grade I TCC. Early results from studies of this marker await verification. Combining some of these new markers may optimize their performance status, allowing the advantages of one test to correct the shortcomings of another. Likewise, their combination with urine cytology may prove beneficial. Although adding urine cytology has not increased the sensitivity of some point-of-service tests, few

studies have addressed the effect on specificity. Until an obvious winner is declared in the race to find a bladder tumor marker, urine cytology will remain the gold standard screening method because of its comfortable familiarity.

Table 3. POTENTIAL MARKERS OF BLADDER CARCINOMA [58]

Test	Detects	Sensitivity	Drawbacks
Bard BTA	Lysed basement membrane components	29% to 40%	Low detection of grade I TCC Poorer predictive value than urine cytology
BTA stat	Human complement factor H-related antigen	67% to 87%	High false-positive with gross hematuria, prostate cancer, BCG
BTA TRAK	Human complement factor H-related antigen	72%	High false-positive with UTI, stones, instrumentation
NMP22	Nuclear matrix proteins	66%	High false-positive with gross hematuria
AuraTek FDP	Fibrinogen, Fibrin/ fibrinogen degradation products	48% to 68%	High false-positive with gross hematuria
Telomerase	Telomerase activity	70%	False-negatives with gross hematuria False-positives with inflammation
Hy aluronic acid	Hyaluronic acid	92%	Too early to substantiate results
Hyaluronidase	Hyaluronidase activity	100Y"	No detection of grade I TCC

BTA = bladder tumor antigen; TCC = transitional cell carcinoma; BCG = bacillus Calmetle-Guerin; UTI = urinary tract infection.

Aims and Objective

1. To assess the accuracy of urinary cytology of voided urine sample in predicting the recurrence of non-muscle invasive transitional cell carcinoma (TCC) of the bladder.

2. To assess the accuracy of urinary cytology of barbotage urine sample in predicting the recurrence of non-muscle invasive transitional cell carcinoma (TCC) of the bladder.

MATERIAL AND METHODS

Study Design: **Prospective Study**

Duration of study: 1st August 2009 to 31st January 2011 (eighteen months)

Patient Characteristics:

One hundred and ninety two patients from the inpatients and outpatients, of the Department of Urology, CMC, Hospital, Vellore, Tamil Nadu were enrolled into the present study.

Inclusion Criteria:

1. Patients with biopsy proven TCC undergoing follow up cystoscopy after initial diagnosis.
2. A functioning bladder, free of any concurrent non-bladder urological cancers.
3. Sterile urine culture.

Exclusion Criteria[8]:

1. Patients with non-bladder urological malignancies.
2. Non-biopsy proven cases.

3. Gross haematuria.

4. Benign inflammatory or untreated infectious conditions.

5. Renal, bladder or ureteric calculi.

6. Recent history of a foreign body in the urinary tract.

7. History of bowel segment interposition in the urinary tract.

Informed consent was taken in all cases. The urine was cultured to detect urinary tract infection. If the culture was positive, an appropriate culture sensitive antibiotic was administered for 5 days.

The study cohorts comprised 192 patients and were followed with office based cystoscopy and voided urinary cytology and barbotage urinary cytology. Of this 192 patients 35 came for review twice, 10 came for review thrice and only one had four reviews. Hence the numbers of cystoscopies were 250 and cytology specimens were 250 of voided urine sample and 250 of barbotage urine sample each. Patients were included at various stages of follow-up and the number of recurrences before inclusion varied from none to several. Voided urine sample and barbotage urine sample for cytology was obtained before cystoscopy.

For voided samples, a midstream collection into a clean container was advised to the patients. No fixatives were added if they were processed immediately. However, an equal amount of 50% ethanol was added as preservative and the specimen was refrigerated if there was delay in processing the urine sample.

Barbotage sample was obtained by washing the bladder through the cystoscope sheath via a 50 cc syringe with 100 cc normal saline. The sample obtained was immediately sent to the laboratory for processing.

Cystoscopy was done with a17 French ACMI or integrated Miller scope under local anesthesia. Suspicious lesions in the bladder were biopsied using a cold cup biopsy forceps or if the tumour was large the patient underwent transurethral resection of the tumour under anaesthesia. . The biopsies were placed in 10% formalin and sent for histopathological examination

Urine sample was centrifuged at a rate of 1800 RPM for thirty minutes and the supernatant urine was discarded. The centrifuged urine sediment was resuspended with 2 drops of bovine albumin mixed well, transferred 0.5ml of this mixture into 2 chambers, and cytospined at 800rpm for 5 minutes After centrifugation the cell sediments at the bottom of the tube was transferred to a glass slide and was stained by the Papanicolaou method and examined under a light microscope. If it is blood stained, Carnoy's fixative was used. By this method, the cytoplasm of transitional cells stains greenish-blue and the nuclei are purple.

The Papanicolaou stained slides were read by a panel of cytopathologist. Malignant and atypical cells were assessed according to the criteria of Koss[45.] Malignant cells showed large hyper chromatic nuclei with coarse chromatin and often occurred in clusters, while atypical cells were regarded as those with enlarged nuclei showing slight to moderate hyperchromasia but not exhibiting the full nuclear abnormalities of malignancy. Specimens were reported as containing

malignant cells, atypical cells, no abnormal cells, or unsuitable for diagnosis. A specimen was judged to be non-diagnostic when there were too few cells present for assessment; the cells were obscured by inflammatory cells or debris or when the specimen was poorly preserved.

The various description of the histopathological examination of the slide were as follows:

Unsatisfactory specimen. This meant that not enough cells or the nontransitional types of cells were found in urine sample.

Negative. This means no cancer cells were identified in urine sample.

Atypical. This indicates some changes were found in the cells in urine sample. But while the cells weren't normal, they weren't abnormal enough to be considered cancer.

Suspicious. This term may indicate that urine cells were abnormal and may be cancerous.

Positive. A positive result indicates that cancer cells were found in urine.

All tumors were graded according to World Health Organization (WHO) 1998 grading[46]. They were staged according to the Tumor Node Metastasis (TNM) system of AJCC[47].

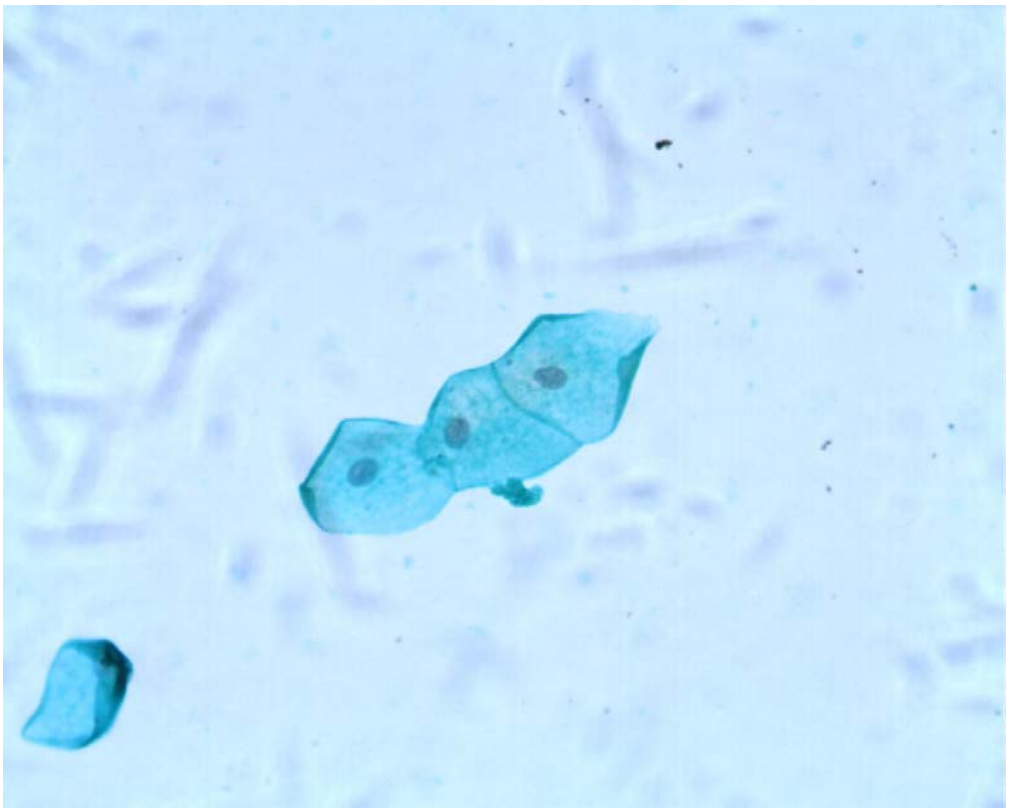


Figure 1. Urine cytology stained by the Papanicolaou procedure. Normal cytology with no mitotic activity and normal nuclear-to-cytoplasmic ratio

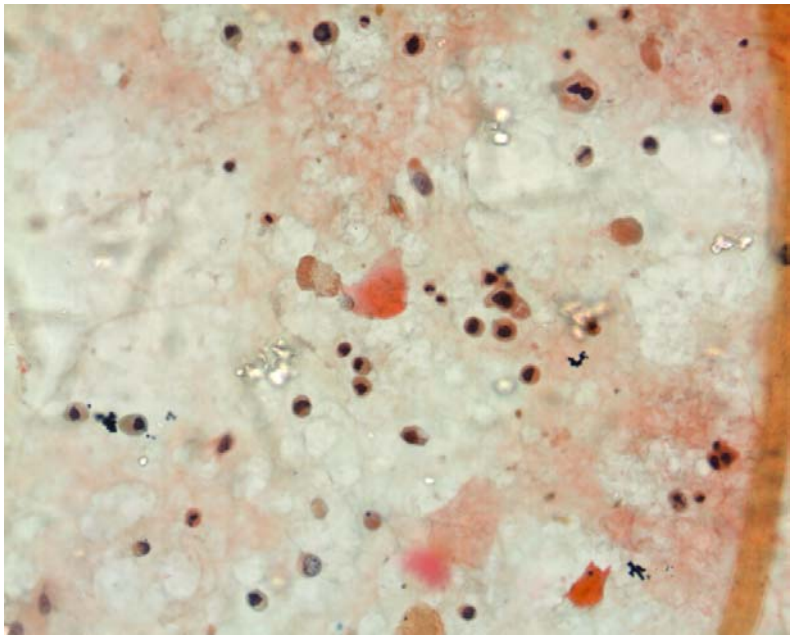


Figure 2. Urothelial cells showing slight atypia with increased nuclear-to-cytoplasmic ratio. Magnification x 40

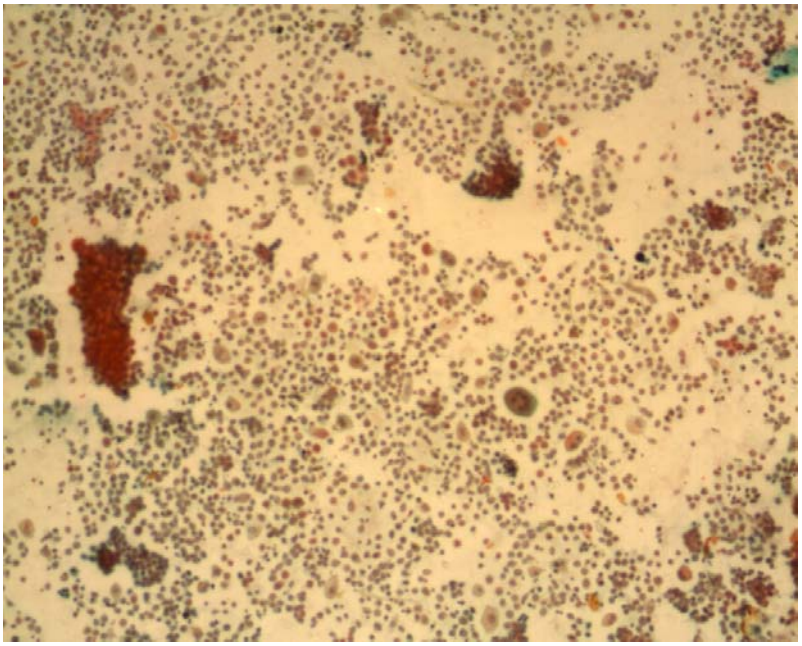


Figure 3. Urothelial cells showing slight atypia with increased nuclear-to-cytoplasmic ratio. Magnification x 10

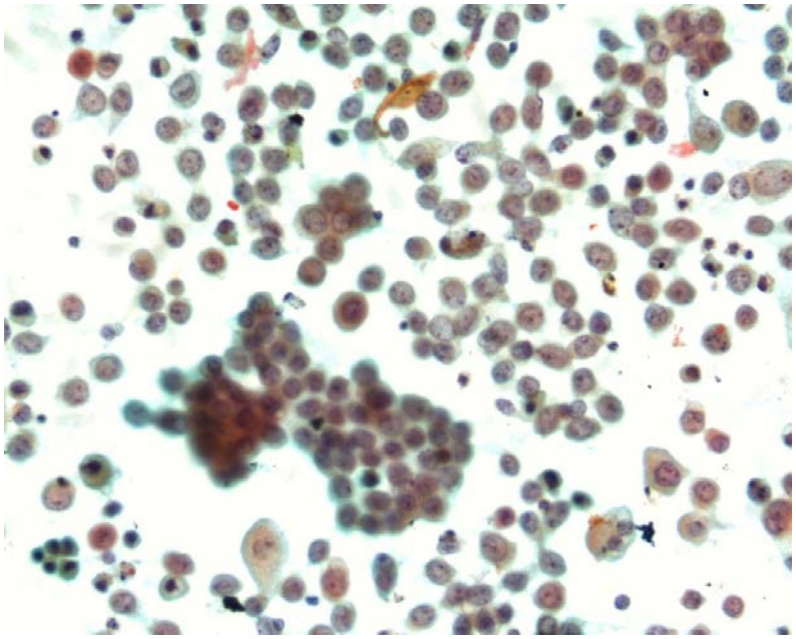


Figure 4. Severe urothelial atypia that is characteristic of bladder cancer, with varying cell size, increased nuclear-to-cytoplasmic ratio and an abnormal chromatin pattern.

OBSERVATIONS AND RESULTS

1. AGE AND SEX DISTRIBUTION

192 patients were enrolled in the study. There were 172 males and 20 females **(Figure: 1)**. The patient's age ranged from 27 to 81 years with a mean age of 55.57 years. The majorities, 71 patients (36.97%), were between 41 -50 years of age **(Table: 1, Figure: 2)**.

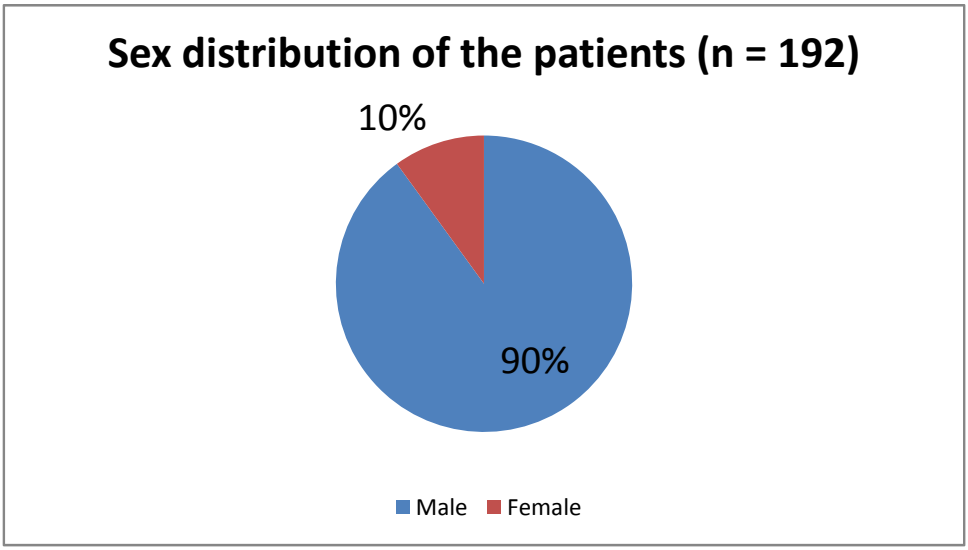


Figure:1

Table: 1 AGE DISTRIBUTION OF THE STUDY POPULATION (n= 192)

Age Range	Number of patients	Percentage
21 -- 30	15	7.81
31 -- 40	43	22.39
41 -- 50	71	36.97
51 -- 60	46	23.95
61 -- 70	13	6.77
71 -- 80	3	1.56
81 -- 90	1	0.52

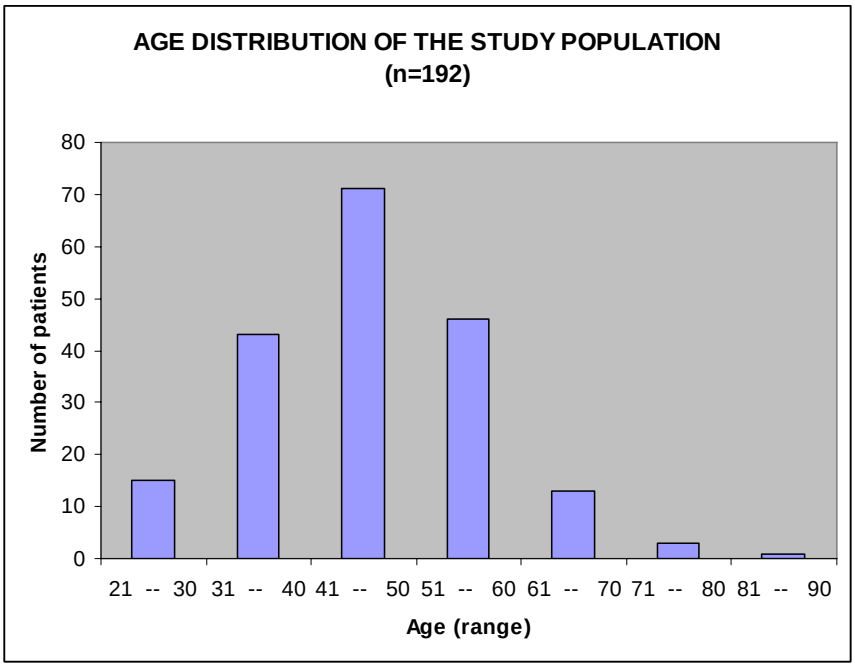


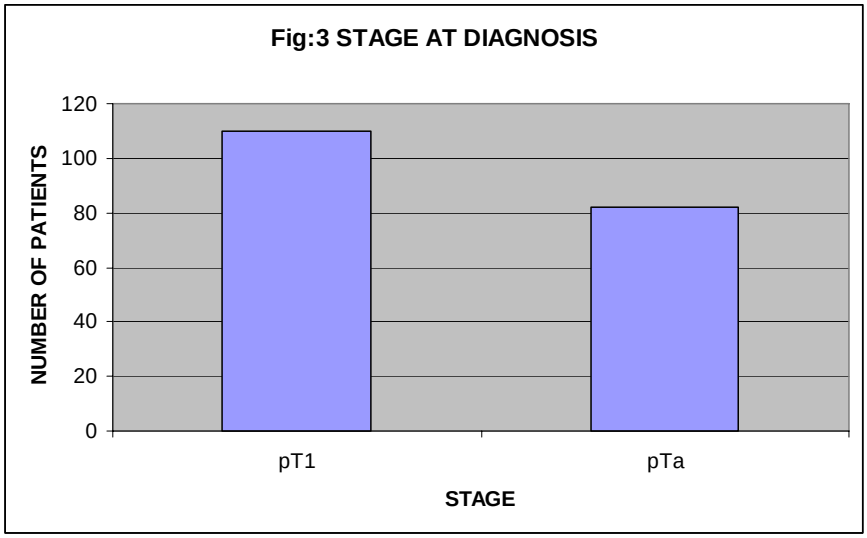
Figure: 2

Stage distribution

All patients had previous, histologically confirmed, TCC with no evidence of muscle invasion (stages Ta, T1 and/or CIS) and were followed with office based cystoscopy and voided urinary cytology. Patients were included at various stages of follow-up and the number of recurrences before inclusion varied from none to several.

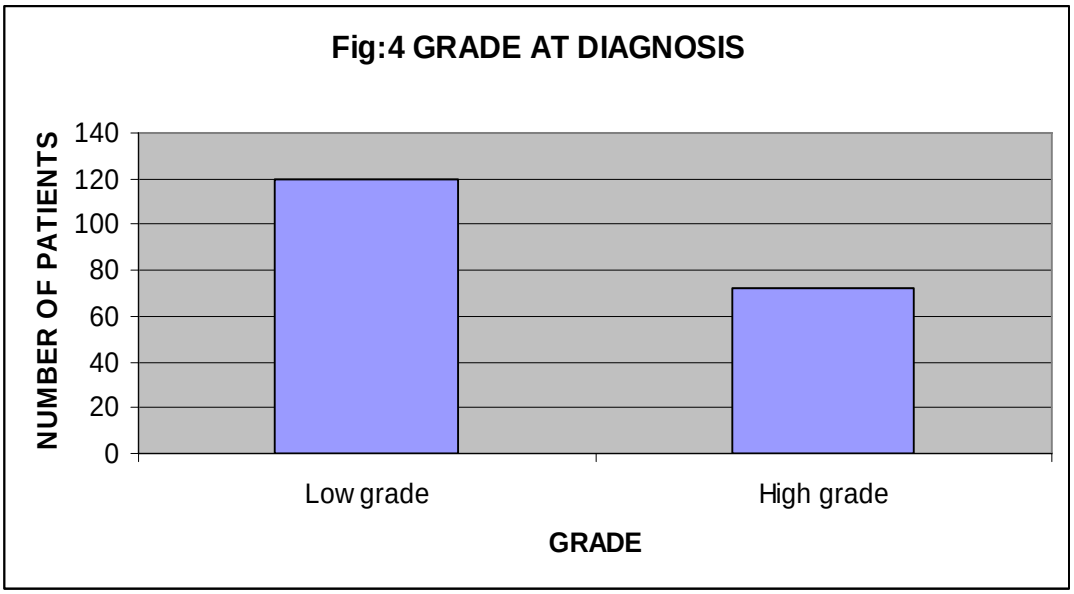
All 192 patients had non-muscle invasive TCC of the bladder.

STAGE AT DIAGNOSIS: Of the 192 patients 82(42.70%) had pTa and 110(57.29%) had pT_1 stage **(Figure: 3)**.



GRADE DISTRIBUTION

INITIAL GRADE DISTRIBUTION: Initially out of the 192 patients, 120(62.5%) patients had a low grade tumour and 72(37.50%) patients had a high grade tumour **(Figure: 4)**. Eighteen patients(25%) with high grade tumour had associated carcinoma in situ.



From 192 patients, 250 assessments met the full criteria for inclusion in the study, providing 250 paired specimens of urine and 250 cystoscopic assessments of the bladder.

Of the 250 cystoscopies, 43 (17%) revealed abnormal mucosa on cystoscopy. The biopsies of which were neoplastic in 31 (72%) specimens, reported as TCC, 7 of the biopsies were reported as chronic cystitis, 3 were reported as BCG cystitis and 2 of the patients who showed small papillary tumours of 2-3 mm were fulgurated and biopsy was not sent. The stage and

grade of the primary tumour and the recurrent tumours were as shown in the table 2.

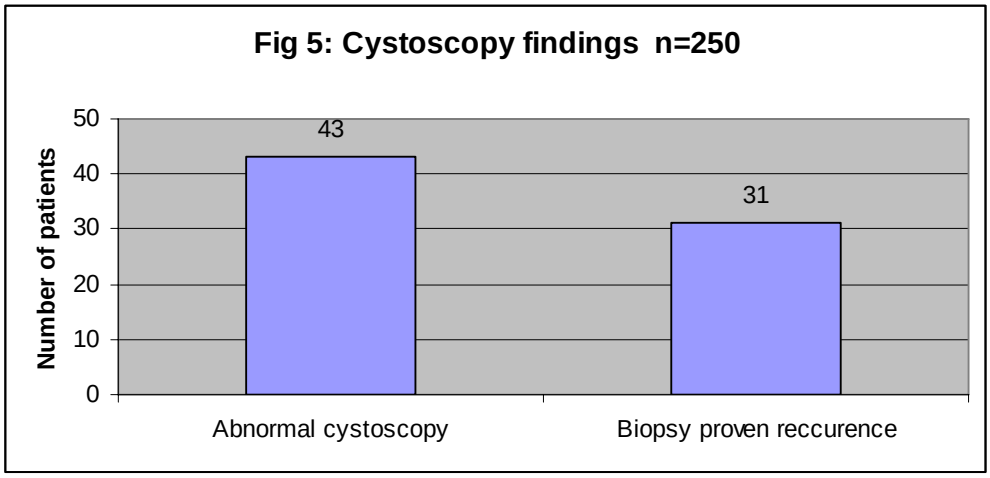


Table:2 Histopathology of the primary and the recurrent tumours (n=31)

Primary tumour	Recurrent tumour	Number of patients (%)
pTaG2	pTaG2	15 (48%)
pT1G2	pT1G2	05 (16%)
PT1G3	pTaG2	01 (3%)
pT1G2	PT1G3	01 (3%)
PT1G3	PT1G3	07 (24%)
PT1G3	CIS	02 (6%)

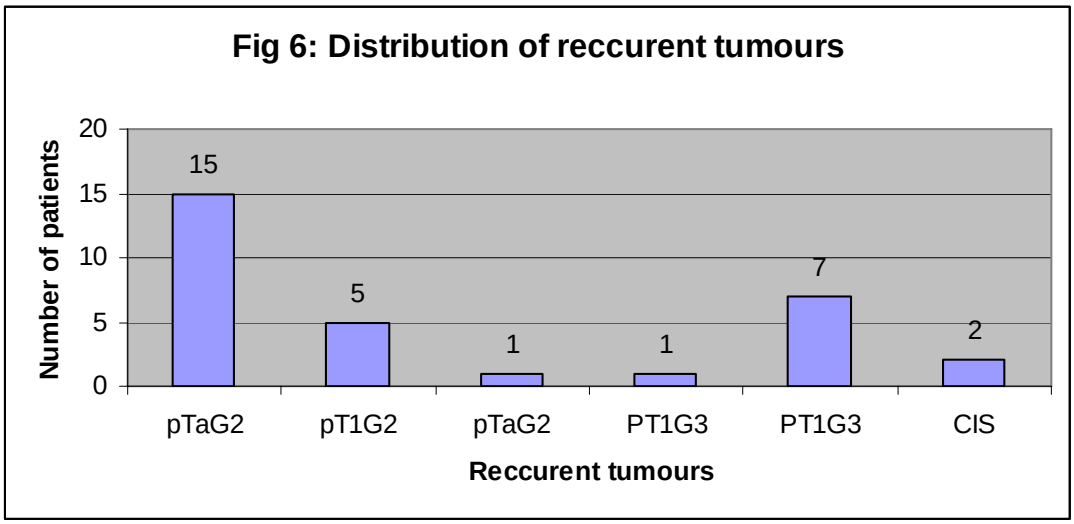


Table:3 Cystoscopically suspicious lesion but negative on HPE n= 12

Chronic cystitis	: 7
BCG cystitis	: 3
Fulguration	
(small tumour not sent for biopsy)	: 2

Table : 4 Sensitivity of the voided and barbotage sample of urine Grade 2 tumours

Stage & grade of recurrent tumor	No. of patients	Positive cystoscopy	Urine cytology positive		Sensitivity	
			Voided sample	Barbotage sample	Voided sample	Barbotage sample
TaG2/T1G2	21	21	5	12	23%	57%

Table : 5 Sensitivity of the voided and barbotage sample of urine Grade 3 tumours and CIS

Stage & grade of recurrent tumor	No. of patients	Positive cystoscopy	Urine cytology positive		Sensitivity	
			Voided sample	Barbotage sample	Voided sample	Barbotage sample
T1G3	8	8	6	4	75%	50%
CIS	2	2	1	1	50%	50%

Table : 6 Sensitivity of the voided and barbotage sample of urine for all grades of tumour

No. of patients with recurrent tumour	Positive cystoscopy	Urine cytology positive		Sensitivity	
		Voided sample	Barbotage sample	Voided sample	Barbotage sample
31	31	12	17	38%	54%

Thirteen samples of voided urine cytology showed atypical cells and ten samples of barbotage urine cytology showed atypical cells in patients with normal cystoscopy. Four voided urine sample and three barbotage urine sample were with scanty cells and unsatisfactory for cytological assessment. Ten of the thirteen samples of voided urine cytology which was false positive were in patient whose primary tumour was T1G3 or multiple recurrence of T1G2 and had received BCG. Eight of the ten samples of barbotage urine cytology which was false positive were also patients with high grade primary tumour who had received BCG. The other five samples (two barbotage and three voided urine sample) which were false positive were in low grade tumors who had not

received any form of intravesical chemotherapy. Upper tract evaluation of the patients with positive urine cytology but negative cystoscopy did not reveal any tumour. They did not manifest TCC even during further follow up.

Fig 7: False positive voided urine cytology

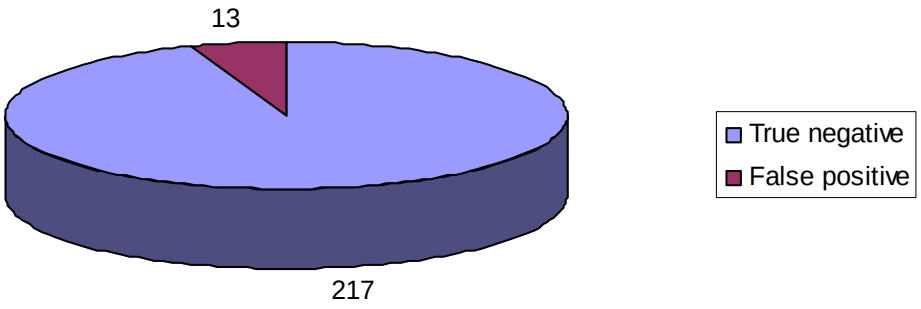
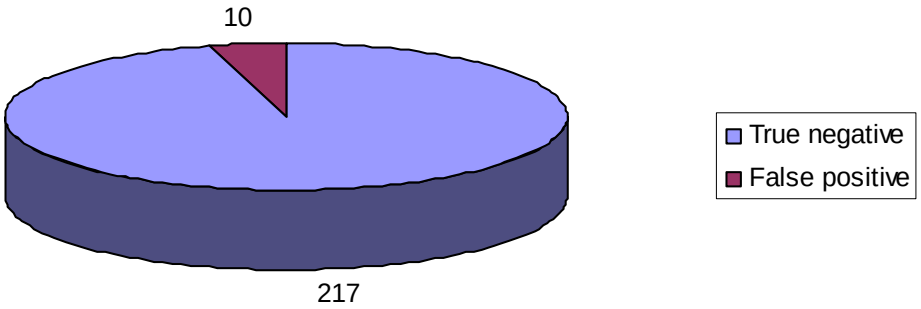


Fig 8: False positive barbotage urine cytology



Specificity of voided urine cytology

True negative	False positive	Specificity (TN/FP+TN)
217	13	92%

Specificity of barbotage urine cytology

True negative	False positive	Specificity (TN/FP+TN)
217	10	95%

Positive predictive value and negative predictive value of voided urine cytology for TaG2/T1G2 tumours n=21

True positive	False negative	True negative	False positive	PPV (TP/TP+FP)	NPV (TN/TN+FN)
5	16	217	13	54%	96%

Positive predictive value and negative predictive value of voided urine cytology for T1G3/CIS tumours n=10

True positive	False negative	True negative	False positive	PPV (TP/TP+FP)	NPV (TN/TN+FN)
7	3	217	13	35%	98%

Positive predictive value and negative predictive value of barbotage urine cytology for TaG2/T1G2 tumours n=21

True positive	False negative	True negative	False positive	PPV (TP/TP+FP)	NPV (TN/TN+FN)
12	9	217	10	54%	96%

Positive predictive value and negative predictive value of barbotage urine cytology for T1G3/CIS tumours n=10

True positive	False negative	True negative	False positive	PPV (TP/TP+FP)	NPV (TN/TN+FN)
5	5	217	10	33%	97%

DISSCUSION

There is an overwhelming propensity of transitional cell carcinoma of the urinary bladder to recur. About 70% of superficial tumours, which are the commonest type, recur within 5 years, 90% in 15 years[6,7]. The greatest challenge in the management of superficial bladder cancer is to prevent progression to invasive disease.

Stage and/or grade progression occurs in a significant number of patients. About 25% of patients with superficial tumours will have recurrences with progression of grade only. These new tumours can continue to be treated transurethrally if they are superficial. Invasive disease requires more aggressive therapy, perhaps finally a radical cystectomy depending on resectability[59]. Around 10%–15% of patients with pT_1 lesions[60] and 2%–4% of patients with pT_a lesions will subsequently have invasion beyond the lamina propria (Stage T_2 or greater) [61].

The management of carcinoma of the bladder has two main goals; to detect relapsing disease before the development of overt symptoms such as gross haematuria and pain, and to identify tumors with potential for early recurrence, invasion or dissemination[1]. Regular surveillance of patients is therefore, imperative.

The current recommendation for cystoscopic surveillance is once every 3 months for the first year, every 6 months for the second year and annually thereafter[9]. It is usually supplemented by urinary cytology which is the standard noninvasive in vitro test to detect recurrence[10]

Cystoscopy continues to be the reference standard for the detection and follow-up of bladder cancer. However, its accuracy can be reduced in certain situations, including poor visualization caused by inflammatory conditions or bleeding, an enlarged median lobe of the prostate, and bladder diverticula. Moreover, small and flat lesions can be difficult to detect and differentiate from other benign bladder lesions.[62,63] Therefore, adjunctive noninvasive tests are used in addition to cystoscopy. Voided urinary cytology has been the most popular and recommended of such tests. In addition to supplementing cystoscopy, it also screens the upper tracts for possible tumor recurrence. However, the sensitivity of urinary cytology is very low, ranging from 11% to 76% and the sensitivity is even lower (15% to 30%) for detecting grade 1-2 bladder tumors. [64, 65] Voided urinary cytology involves visual assessment of morphologic changes and, therefore, requires intact cells. Small tumors or well-differentiated tumors, or both, are less likely to exfoliate cells spontaneously, because the strong intercellular attachments are better preserved and the degree of morphologic departure from normal is less, making recognition difficult. [66] This results in a low sensitivity of 15% to 30% for early-stage cancer. [67, 68] The factors affecting the sensitivity of urinary cytology include specimen quality, number of exfoliated cells, and pathologist expertise. Also, inflammatory conditions of the bladder can confound the results.

Despite high specificity, it is not possible to localize cancer based on urine cytology alone. Therefore, a positive test result always needs further investigations. A normal looking bladder on cystoscopy and negative bladder biopsy however, doesn't exclude possibility of urothelial cancer. In positive urine cytology cases with normal bladder biopsy, imaging and cystoscopy should be

repeated since a bladder or upper urinary tract cancer may be subsequently detected [58.69,70]. There are several other factors such as reactive changes secondary to infection, stone, previous instrumentation and intravesical therapy which are responsible for majority of false diagnosis [68.]

It is important to provide relevant clinical information (including instrumentation, previous treatment and the method of urine collection) in order to enable the cytopathologist to report with greater accuracy[68]

Urinary cytology has been considered the gold standard in bladder cancer screening [58]. Recent advances in diagnostic methods are challenging its usefulness. This study compared urinary cytology with pathologic findings of proven bladder cancer patients to determine the value of voiding and barbotage urinary cytology.

The mean age of the patients being 55.57 years in the present study, is consistent with the fact that, though carcinoma bladder can occur at any age, it is generally a disease of middle age and the elderly. Lynch and Cohen[3] reported a median age at diagnosis of TCC of 69 years in males and 71 years in females. In adolescents and adults younger than 30 to 40 years, bladder cancers tend to express well differentiated histology and behave in a more indolent fashion[9].

TCC of the bladder is 2.5 to 4 times commoner in men than in women[2,3]. The higher rates for males remain high even after adjustment for cigarette smoking and exposure to occupational carcinogens. Possible explanations for the excessive risk in males include environmental and dietary factors not yet identified and innate sexual characteristics, such as hormonal factors[71]. The sex

distribution in this study was a male: female ratio of 8.6:1.The study population was, consisting solely of patients on follow up.

The mean (range) sensitivity of urinary cytology for high-grade bladder tumours is 90% [22, 26] and the specificity reaches 98% to 100%.[22, 26] the accuracy of urine cytology appears to be associated with considerable variability. Positive results are obtained in 31–72% of patients with bladder cancer, when all tumour grades and stages are considered [11-20]. Cytology has shown high accuracy in detecting high-grade TCC; its performance has been inconsistent in detecting low-grade lesions [13]. Tumour grade represents the foremost determinant of the performance characteristics of urinary cytology. The predictive accuracy of cytology is also influenced by differences in the preparation techniques of smears, suboptimal specimen quality, and the interpretative experience and skill of the cytopathologist [17].

In the present study the sensitivity of voided urine cytology for high grade tumour was 60% and for low grade tumours it was 23% and the specificity was 92%. The sensitivity of barbotage urine cytology for high grade tumour was 50% and for low grade tumours it was 57% and the specificity was 95%.Urine cytology was read by five different pathologist. Poor to intermediate interobserver agreement among cytologists confirms the importance of operator bias [72]. The present patients had appreciable heterogeneity of the risk variables, recurrence rates, and stages and grades of recurrent tumours. We did not use central pathology and cytology reviews. Therefore, the observed poor sensitivity may stem from differences in cytomorphological specimen interpretation, specimen quality, and the interpretative experience and skill of the cytopathologists. The

pathologists and cytopathologists were unaware of patient clinical characteristics, which might have decreased their ability to accurately interpret the cytomorphological findings.

The low sensitivity of both voided and barbotage urine cytology regardless of tumour stage and grade, contradicts the accepted thought that cytology always performs well in high-grade and advanced-stage tumours. Our data provide a realistic assessment of the yield of urinary cytology which may reflect interpretative experience and skill of the cytopathologists.

The comparison of sensitivity of the present study with the results of other studies are given in the table below

References	No. of Pts	Grade	% pos.cytology	% pos.bladder washings
Harris et al [38]	20	2	40	80
		3	60	100
Eposti et al [39]	195	1	-	28
		2	-	76
		3	-	89
National bladder cancer Collaboration Group A[40]	114	1	13	40
		2	39	35
		3	77	88
MacFarlane, Ceelen, Taylor et al [41]	119	Low	55	-
		High	88	-
Dubernard, Devonec, Amiel, Bouvier et al [42]	51	1	9	-
		2	75	-
		3	93	-
Tawfik Zein et al [37]	73	1	25	31
		2	57	85
		3	74	87
Present study	192	Low	23	57
		High	70	50

The specificity of voided and barbotage urine cytology were 92% and 95% respectively in the present study. Ten of the thirteen samples of voided urine cytology which was false positive were in patient whose primary tumour was T1G3 or multiple recurrence of T1G2 and had received BCG. Eight of the ten samples of barbotage urine cytology which was false positive were also patients with high grade primary tumour who had received BCG. The other five samples (two barbotage and three voided urine sample) which were false positive were in low grade tumors who had not received any form of intravesical chemotherapy.

In a prospective study done by Kapila et al [73] the specificity of urine cytology was 87% for all grade tumours and it has ranged from 98-100%[58] depending on the grade of the tumour.

Positive predictive value of voided urine cytology for TaG2/T1G2 tumours and T1G3/CIS tumours were 54% and 34% respectively. The negative predictive value of voided urine cytology for TaG2/T1G2 tumours and T1G3/CIS tumours were 96% and 98% respectively.

Positive predictive value of barbotage urine cytology for TaG2/T1G2 tumours and T1G3/CIS tumours were 54% and 33% respectively. The negative predictive value of barbotage urine cytology for TaG2/T1G2 tumours and T1G3/CIS tumours were 96% and 97% respectively.

The positive predictive value (PPV) results too differ widely in different studies. The lowest of 13% was reported by Konety et al[74] and Renshaw et al [31] reported a positive predictive value 59% to 66%.

Several factors contribute to this poor ability of urine cytology to detect cancer cells: only a small sample of urine can be processed and only a fraction of the sample can be used for final analysis which reduces the chance of capturing tumor cells. Background cells such as erythrocytes and leukocytes also confound the cytologic technique [18]. Furthermore, cytologic criteria that differentiate between low grade tumors and reactive cells can be ambiguous. In the follow up of bladder cancer, the low sensitivity of urine cytology limits its use as a detection tool.

The Future of Cytologic Urinanalysis

Improvements in Sample Preparation

Efforts are underway to design faster, inexpensive and more sensitive point-of-care sample collection and preparation techniques that will significantly improve platforms on which routine and specialized urine cytopathologic tests are performed. The recent fabrication of a parylene membrane micro filter device that can capture circulating tumor cells from the blood of cancer patients by employing the principle of inherent differences in tumor cell size compared to normal blood cells [75] is also being evaluated for capture and characterization of exfoliated urothelial tumor cells from patient urine. The unique and precise engineering of the microfilter device allows enrichment of exfoliated tumor cells on a small surface area while eliminating background erythrocytes and leukocytes that typically confound routine urine cytologic specimens. This platform has shown promise in bladder cancer surveillance, and it is conceivable

that this can also be used for on-site bladder cancer detection protocols in the future.

Automated Image Cytometry

Abnormalities in DNA ploidy and nuclear shape are characteristic of tumor cells. While cytologists rely on identification of these changes in urine specimens, automated image analysis now allows identification of these changes on a more objective scale. The Quanticyt system employs image analysis to identify DNA ploidy abnormalities and nuclear morphometry [76]. The karyometric system is based on two nuclear features: the 2c-deviation index (2cDI) and the mean of a nuclear shape feature, MPASS . Samples are scored as low, intermediate, or high-risk that has been determined by correlation with histology data. A study has shown that prediction of a cystoscopic lesion by routine cytology and Quanticyt was comparable, and the latter was superior for predicting tumor recurrence after normal findings at cystoscopy [77]. Another group has employed artificial intelligence to develop a neural network-based digitized cell image diagnosis system that identifies potentially abnormal cells in bladder washes by algorithmic analysis [78]. The selected digitized cell images are reanalyzed by two independent neural networks; one is trained to select single cancer cells and the other one cancer cell clusters, regardless of cell shape, overlapping, or staining. The selected cells or cell clusters are displayed on a high-resolution Computer screen for evaluation by a cytopathologist. The Quanticyt system has shown a sensitivity of 59%-69%, and specificity of 72.5%-93% in detecting bladder cancer [79, 80]. It has also been suggested that employment of Quanticyt to analyze consecutive bladder washes can increase the detection rate of invasive disease in samples

that are labeled high-risk [81]. In a pilot study, the neural network-based diagnosis system showed 92% sensitivity in diagnosing histologically confirmed tumors, as opposed to 69% for Quanticyt and 50% for routine cytology [78]. While the major advantage of these cytometric analyses is label-free quantification that closely mimics the routine cytology procedure, a drawback is the need for a bladder wash sample instead of voided urine.

SUMMARY AND CONCLUSIONS

Transitional cell carcinoma of the bladder is a common malignant neoplasm affecting both men and women. Nonmuscle invasive TCC (about 70% of the affected population) is a chronic illness with no definite curative measures. However, patients with these tumors have excellent survival rate. Therefore, the main goal in their management is to diagnose the primary and recurrent tumors as early as possible and treat them.

Follow up cystoscopy is the gold standard for surveillance of this tumor. But it is expensive and invasive. The other non-invasive method is voided urine cytology which is less sensitive when compared with cystoscopy especially in picking up low stage, low grade lesions. And all the guidelines do recommend urine cytology during the follow up of all patients with nonmuscle invasive TCC.

Few studies[21, 23, 25] have found the barbotage urine cytology to have better yield than voided urine cytology in the follow up of non-muscle invasive TCC bladder. Based on this background, we studied 192 patients with nonmuscle invasive TCC of the bladder in a prospective manner to assess the sensitivity of voided and barbotage urine cytology in the diagnosis of nonmuscle invasive TCC. We made the following observations.

1. Out of 192 patients 172 were male and 20 were female, most of the patients were in their 4^{th} or 6^{th} decade of life.

2. Initially, Of the 192 patients 82(42.70%) had pTa and 110(57.29%) had pT_1 stage

3. The grade of the initial (primary) tumours were low grade in 120(62.5%) and high grade in 72(37.5%).

4. For 192 patients, 250 review cystoscopies were done and 31(12.4%) had histologically proven recurrence.

5. Among the recurrent tumors 16(51.61%) patients had pTa lesions 13(41.93%) patients had pT_1 tumours, 2(6.45%)patients had CIS

6. Histological grade of the recurrent tumour was grade 2 in 21(67.74%) patients; grade 3 in 8 (25.8%) patients and CIS in 2 (6.45%) patients.

7. Sensitivity of the barbotage urine cytology was 57% in low grade tumour when compared to voided urine cytology which was 23%.

8. Sensitivity of the barbotage urine cytology was 50% in high grade tumour when compared to voided urine cytology which was 70%.

9. Overall sensitivity, specificity, positive predictive value, negative predictive value of the voided urine cytology was 38.75%, 92%, 48% and 91% respectively.

10. Overall sensitivity, specificity, positive predictive value, negative predictive value of the barbotage urine cytology was 54.83%, 95%, 62% and 93% respectively.

11. Patients with positive urine cytology (voided or barbotage) but negative cystoscopy did not show TCC in the upper tract making these tests truly false positive.

Conclusion

Cystoscopy, the current gold standard for bladder cancer detection, and follow up of TCC bladder exhibits high sensitivity and specificity will continue with its numero uno status. Urine cytology is an established method and there is sufficient evidence to show its high specificity. However the method suffers from low sensitivity.

In the present study the sensitivity of 23% and 57% for the voided and barbotage urine cytology respectively strongly questions the need for these tests during the follow up.

There would be no harm done if urine cytology is discontinued as a test for TCC bladder during the follow up of low grade nonmuscle invasive TCC.

Barbotage urine cytology showed higher sensitivity than voided urine cytology, but was not significant enough to recommend for follow up of the TCC bladder. Also barbotage urine cytology is invasive and in it self can cause changes in the morphology of the cells[68] affecting its sensitivity.

In conclusion one could safely discontinue the protocol of urine cytology in the follow up of low grade TCC bladder as cystoscopy which is more sensitive is mandatory and is the standard of care during the follow up of TCC bladder. Barbotage urine cytology also showed poor sensitivity. In this study the barbotage urine cytology sensitivity (50%) was lower than the voided urine cytology (70%) for high grade tumours which was contrary to all the previous studies [21, 22, 23]. Also it is an invasive test which can increase the morbidity by introducing infection and it is better if one can avoid this invasive test with poor sensitivity.

BIBLIOGRAPHY

1. Halachmi S, Linn JF, Amiel GE, Moskovitz B, Nativ O. Urine cytology, tumour markers and bladder cancer. Br J Urol 1998; 82: 647- 654.

2. Greenlee RT, Murray T, Bolden S, Wings PA .Cancer Statistics. CA Cancer J Clinic 2000; 50: 7-15

3. Lynch CF, Cohen MB. Urinary System. Cancer 1995; 75(Suppl): 316 - 324.

4. Konety BR, Nguyen TST, Dhir R, Day RS, Becich MJ, Stadler WM, et al. Detection of bladder cancer using a novel nuclear matrix protein BLCA-4. Clin Cancer Res 2000; 6: 2618-2625

5. Bostwick DG, Ramnani D, Cheng L. Diagnosis and grading of bladder cancer and associated lesions. Urol Clin North Am 1999; 26(3): 493 - 507.

6. Carpinito GA, Stadler WM, Briggman JV, Chodak GW, Church PA, Lamm DL, et al. Urinary nuclear matrix protein as a marker for transitional cell carcinoma of the urinary tract. J Urol 1996; 156: 1280 - 1285.

7. Sanchez-Carbayo M, Herrero E, Megias J, Mira A, Soria F. Comparative sensitivity of urinary CYFRA-21-1, urinary bladder cancer antigen, tissue polypeptide antigen and NMP-22 to detect bladder cancer. J Urol 1999; 162: 1951 - 1956.

8. Sharma S, Zippe CD, Pandrangi L, Nelson D, Agarwal A. Exclusion criteria enhance the specificity and positive predictive value of NMP-22 and BTA Stat. J Urol 1999; 162: 53 - 57.

9. Messing EM. Urothelial tumours of the Urinary tract. In: Walsh PC, Retik AB, Vaughan ED, Wein AJ, editors. Campbell's Urology.8th edition. Pennsylvania; 2002 p. 2732 - 2784.

10. Saad A, Hanbury DC, McNicholas TA, Boustead GB, Woodman AC. The early detection and diagnosis of bladder cancer: A critical review of the options. Eur Urol 2001; 39: 619 - 633.

11. Umiker W**.** Accuracy of diagnosis of cancer of the urinary tract. Acta Cytol 1964;8: 186–93

12. Schoonees R, Gamarra MG, Moore RH, Murphy GP**.** The diagnostic value of urinary cytology in patients with bladder carcinoma.J Urol1971;106: 693–6

13. Rife CC, Farrow GM, Utz DC. Urine cytology of transitional cell neoplasms. Urol Clin North Am 1979;6 : 599–612

14. Kern WH. The grade and pathologic stage of bladder cancer. Cancer 1984;53:1185–9

15. Koss LG, Deitch D, Ramanathan R, Sherman AB**.** Diagnostic value of cytology of voided urine. Acta Cytol 1985;29: 810–6

16. Badalament RA, Kimmel M, Gay H *et al.* The sensitivity of flow cytometry compared with conventional cytology in the detection of superficial bladder carcinoma.*Cancer*1987;60: 1423–7

17. Bastacky S, Ibrahim S, Wilczynski SP, Murphy WM.The accuracy of urine cytology in daily practice.Cancer 1999;87: 118–28

18. Wiener HG, Vooijs GP, van't Hof-Grootenboer B**.** Accuracy of urinary cytology in the diagnosis of primary and recurrent bladder cancer.Acta Cytol 1993;37: 163–9

19. Zein TA, Milad MF**.**Urine cytology in bladder tumors. Int Surg1991;76:52–4

20. Raitanen MP, Aine R, Rintala E *et al.*Differences between local and review urinary cytology diagnosis of bladder cancer. An interobserver multicenter analysis. Eur Urol 2002;41:284–9

21. Badalament RA, Hermansen DK, Kimmel M, et al: The sensitivity of bladder wash flow cytometry, bladder wash cytology, and voided cytology in the detection of bladder carcinoma. Cancer 60:1423-1427, 1987

22. DeMay RM: Urine. *In* The Art & Science of Cytopathology. Chicago, ASCP Press, 1996

23. Gregoire M, Fradet Y, Meyer F, et al: Diagnostic accuracy of urinary cytology, and deoxyribonucleic acid flow cytometry and cytology on bladder washings during follow up for bladder tumors. J Urol 1571160-1664, 1997

24. Grossman HB: New methods for detection of bladder cancer. Semin Urol Oncol 16:17-22, 1998

25. Leyh H, Hall R, Mazeman E, et al: Comparison of the Bard BTA test with voided urine and bladder Wash cytology in the diagnosis and management of cancer of the bladder. Urology 50:49-53, 1997

26. Murphy WM, Soloway MS, Jukkola AF, et al: Urinary cytology and bladder cancer: The cellular features of transitional cell neoplasms. Cancer 53:1555-1565,1984

27. Papanicolaou GN, Marshall VF: Urine sediment smears as a diagnostic procedure in cancers of the urinary tract. Science 101:519-520, 1945

28. Raab SS, Lenel JC, Cohen MB: Low grade transitional cell carcinoma of the bladder: Cytologic diagnosis by key features as identified by logistic regression analysis. Cancer 74:1621-1626, 1994

29. Raab SS, Slagel DD, Jensen CS, et al: Transitional cell carcinoma: Cytologic criteria to improve diagnostic accuracy. Mod Pathol 9225-232, 1996

30. Ramakumar S, Bhuiyan J, Besse JA, et al: Comparison of screening methods in the detection of bladder cancer. J Urol 161:388-394, 1999

31. Renshaw AA, Nappi D, Weinberg DS. Cytology of grade 1 papillary transitional cell carcinoma. A comparison of cytologic, architectural and morphometric criteria in cystoscopically obtained urine. Acta Cytol. 1996 Jul-Aug;40(4):676-82.

32. Zein TA, Milad MF urine cytology in bladder tumors. Int Surg. 1991 Jan-Mar;76(1):52-4.

33. Mungan NA, Kulacoglu S, Basar M, Sahin M, Witjes JA. Can sensitivity of voided urinary cytology or bladder wash cytology be improved by the use of different urinary portions? Urol Int. 1999;62(4):209-12.

34. Robert S, Svatek, David Lee, and Yair Lotan Correlation of office-based cystoscopy and cytology with histologic diagnosis: How good is the reference standard? Urology 2005. 66**:** 65–68,

35. Karakiewicz PI, Benayoun S, Zippe C, Lüdecke G, Boman H, Sanchez-Carbayo M, Casella R, Mian C, Friedrich MG, Eissa S, Akaza H, Huland H, Hedelin H, Rupesh R, Miyanaga N, Sagalowsky AI, Marberger MJ, Shariat SF Institutional variability in the accuracy of urinary cytology for predicting recurrence of transitional cell carcinoma of the bladder. BJU Int. 2006 May;97(5):997-1001. Epub 2006 Mar 17.

36. Loh CS, Spedding AV, Ashworth MT, Kenyon WE, Desmond AD. The value of exfoliative urine cytology in combination with flexible cystoscopy in the diagnosis of recurrent transitional cell carcinoma of the urinary bladder.Br J Urol. 1996 May;77(5):655-8.

37. Tawfik zein, Zev Wajsman, Lenore S, Englander, Marie Gamarra, Cecilia Lopez, Robert P, Huben and Edson Pontes, Evaluation of bladder washings and urine cytology in the diagnosis of bladder cancer and its correlation with selected biopsies of the bladder mucosa, The Journal of Urology, 1984:132, 670-673.

38. Harris MJ, Schwinn CP, Marrow JW, Gray RL, and Browell BM, Exfoliative cytology of the urinary bladder irrigation specimen.Acta Cytology:1972,15, 385-187

39. Eposti PL, Moberger G, Zajick J, The cytological diagnosis of transitional cell tumours of the urinary bladder and its histological basis. Astudy of 567 cases of urinary tract disorder including 170 untreated 182 irradiated bladder tumours.Acta cytology: 1970,14,145

40. National Bladder cancer Collaborative Group A: Cytology and histopatholgy of bladder cancer cases in a prospective longitudinal study.Cancer Res.,1977;37,2911

41. MacFarlane EWE, Ceelen GH, Taylor JN, Acta Cytol.,1964:8.288

42. Dubernard JM, Devonec M, Amiel J, Bouvier R, Fontaniere B, Faucon M, European Urology 1982: 8, 5-9

43. Trott PA, Edwards L, Comparison of bladder washings and urine cytology in the diagnosis of bladder cancer.J Urol 1973:110, 664

44. Flanagan MJ, Miller A, III: Evaluation of bladder washing cytology for bladder cancer surveillance J Urol 1978:119, 42

45. Koss LG Tumours of the urinary tract and prostate. In Koss LG ed Diagnostic cytology and its histopathologic bases, 3rd edn, Vol.II. London: JB Lippincott Company, 1979: 749-817

46. Epstein JI, Amin MB, Reuter VE, Mostofi FK and the bladder consensus conference committee. The World Health Organization / International Society Of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. Am J Surg Pathol1998; 22(12): 1435 -1448.

47. Greene FL, Page DL, Fleming ID, Fritz AG, Balch CM, Haller DG et al, eds. AJCC Cancer Staging Manual, 6th Ed. AJCC Springer - Verlag, New York, Berlin, Heidelberg; 2002, p. 335 - 340.

48. Sanders WR: Cancer of the bladder: fragments forming urethral plugs discharged in urine—concentric colloid bodies. Edinburgh Med J 10: 273–275, 1864.

49. Dickenson WH: Portions of cancerous growth passed by urethra. Trans Pathol Soc London 20: 233–235, 1869.

50. Kris E, Gaston, Raj S, Pruthi Value of urinary cytology in the diagnosis and management of urinary tract malignancies Urology, 2004: 63: 1009–16,

51. Koss LG, Deitch D, Ramanathan R, *et al:* Diagnostic value of cytology of voided urine. Acta Cytol 29: 810–814,1985.

52. Bastaky S, Ibrahim S, Wilczynski SP, *et al:* The accuracy of urine cytology in daily practice. Cancer (Cancer Cytopathol) 87: 118–128, 1999.

53. Murphy WM, Soloway MS, Jukkola AF, *et al:* Urinary cytology and bladder cancer: cellular features of transitional cell neoplasms. Cancer 53: 1555–1565, 1984.

54. Papanicolaou GN, and Marshall VF: Urine sediment smears as a diagnostic procedure in cancers of the urinary tract. Science 101: 511–519, 1945.

55. Badalament RA, Hermansen DK, Kimmel M, *et al:* The sensitivity of bladder wash flow cytometry, bladder wash cytology,and voided cytology in the detection of bladder carcinoma. Cancer 60: 1423–1427, 1987.

56. Cajulis RS, Haines GK III, Frias-Hidvegi D, *et al:* Cytology, flow cytometry, image analysis, and interphase cytogenetics by fluorescence in situ hybridization in the diagnosis of transitional cell carcinoma in bladder washes: a comparative study. Diagn Cytopathol 13: 214–223, 1995.

57. Gregoire M, Fradet Y, Meyer F, *et al:* Diagnostic accuracy of urinary cytology, and deoxyribonucleic acid flow cytometry and cytology on

bladder washings during followup for bladder tumors. J Urol 157: 1660–1664, 1997.

58. Felix M. Brown, Urine cytology Is it Still the Gold Standard for Screening? UCNA, volume 27, (1), February 2000

59. Gilbert HA, Logan JL, Kagan AR, Friedman HA, Loye JK, Fox M, et al. The natural history of papillary transitional carcinoma of the bladder and its treatment in an unselected population on the basis of histological grading J Urol 1978; 119: 488 – 497.

60. Lutzeyer W, Ruebben H, Dahou H. Prognostic parameters in superficial bladder cancer: an analysis of 315 cases. J Urol 1982; 127: 250 – 256.

61. Fitzpatrick JM, West AB, Butler MR, Lane V, O' Flynn JD. Superficial bladder tumours (Stage $_{p}$T grade 1 and 2): The importance of recurrence pattern following initial resection. J Urol 1986; 135: 920 – 926

62. Frimberger D, Zaak D, and Hofstetter A: Endoscopic fluorescence diagnosis and laser treatment of transitional cell carcinoma of bladder. Semin Urol Oncol 18: 264–272, 2000.

63. Hudson MA, and Herr HW: Carcinoma in situ of the bladder. J Urol 153: 564–572, 1995.

64. Lokeshwar VB, and Soloway MS: Current bladder tumor tests: does their prolonged utility fulfill clinical necessity? J Urol 165: 1067–1077, 2001.

65. Al Sukhun S, and Hussain M: Molecular biology of TCC. Crit Rev Oncol Haematol 47: 181–193, 2003.

66. Farrow GM: Urine cytology in the detection of bladder cancer: a critical approach. J Occup Med 32: 817–821, 1990.

67. Badalament RA, Hermansen DK, Kimmel M, *et al:* The sensitivity of bladder wash flow cytometry, bladder wash cytology, and voided cytology in the detection of bladder carcinoma. Cancer 60: 1423–1427, 1987.

68. Viswanath S, Zelhof B, et al. Is routine urine cytology useful in the haematuria clinic?. Ann R Coll Surg Engl 2008; 90: 153–155.

69. Kimura Y, Takahashi A, Hirobe M, Kunishima Y, Masumori N, Matsukawa M, et al. Patients with clinically unconfirmed positive urinary cytology - retrospective analysis

70. Frable WJ, Paxson L, Jo A. Barksdale Jo A, Warren W. Koontz Jr. Current practice of urinary bladder cytology. Cancer Researh. 1977;37(8 Pt 2):2800-2805

71. Hartage P, Harvey EB, Linehan WM, Silverman BT, Sullivan JW, Hoover RN, et al. Unexplained risk of bladder cancer in men. J Natl Cancer Inst 1990; 82: 1636 – 1640.

72. Paez A, Coba JM, Murillo N *et al.*Reliability of the routine cytological diagnosis in bladder cancer. Eur Urol 1999;35: 228–32

73. Kapila K, Kehinde EO, Anim JT, Mojiminiyi OA, Vinsu A, George SS, Al-Maghrebi M, Al-Mulla F. Could nuclear matrix protein 22 (NMP22) play a role with urine cytology in screening for bladder cancer?--experience at Kuwait University.Cytopathology. 2008 Dec;19(6):369-74. Epub 2008 Jul 9.

74. Konety BR, Metro MJ, Melham MF, Salup RR.Diagnostic value of voided urine and bladder barbotage cytology in detecting transitional cell carcinoma of the urinary tract. Urol Int. 1999; 62(1):26-30.

75. Zheng S, Lin H, Liu JQ, Balic M, Datar R, Cote RJ, et al. Membrane microfilter device for selective capture, electrolysis and genomic analysis of human circulating tumor cells. J Chromatogr *A.* 2007 Aug 31; 1162(2):154-61.

76. van der Poel HG, Witjes JA, van Stratum P, Boon ME, Debruyne FM, Schalken JA. Quanticyt: karyometric analysis of bladder washing for patients with superficial bladder cancer. Urology. 1996 Sep; 48(3):357-64

77. van der Poel HG, Boon ME, van Stratum P, Ooms EC, Wiener H, Debruyne FM, et al. Conventional bladder wash cytology performed by four experts versus quantitative image analysis. Mod Pathol. 1997 Oct; 10(10):976-82.

78. Vriesema JL, van der Poel HG, Debruyne FM, Schalken JA, Kok LP, Boon ME. Neural network-based digitized cell image diagnosis of bladder wash cytology. Diagn Cytopathol. 2000 Sep;23(3):171-9.

79. van der Poel HG, van Balken MR, Schamhart DH , Peelen P, de Reijke T, Debruyne FM, et al. Bladder wash cytology, quantitative cytology, and the qualitative BTA test in patients with superficial bladder cancer. Urology. 1998 Jan; 51(1):44-50.

80. Wiener HG, Mian C, Haitel A, Pycha A, Schatzl G, Marberger M. Can urine bound diagnostic tests replace cystoscopy in the management of bladder cancer? J Urol. 1998 Jun; 159(6):1876-80.

81. van der Poel HG, van Rhijn BW, Peelen P, Debruyne FM, Boon ME, Schalken JA. Consecutive quantitative cytology in bladder cancer. *U*rology. *2*000 Oct 1; 56(4):584-8.

Informed consent document

The Department of Urology at CMC, Vellore is conducting a study on voided urine and barbotage urine cytology in the patients with non muscle invasive TCC of bladder on follow up.

It is a diagnostic test which involves giving a sample of voided urine for evaluation of malignant cells or any other abnormal cells. The barbotage sample is collected at the time of cystoscopy which will be done on all the patients on follow up for the TCC bladder.

If you agree to participate in this study, the doctor will ask you to deposit one freshly voided urine sample in the cytology laboratory on the day planned for cystoscopy. The barbotage urine sample will be collected during the cystoscopy and will be sent to cytology laboratory by our staff. The results of these tests will be conveyed to you and the possible implications if any will be explained to you.

Your decision not to participate in the study will not affect the care you will receive at the hospital in any way. Even if you do agree to become a study participant, you can withdraw from the study at any time without affecting the care that you will receive. The study is likely to expose you to urinary tract infection. The barbotage will not further increase the discomfort that occurs during the cystoscopy.

There will be no immediate benefits from your participation in this study. This study will help us to determine the value of the cytology in follow up of TCC bladder. There will be no monetary compensation for this study, but the cost of this study will be born by the institute.

The records concerning your participation are to be used only for the purpose of this research project. Any information obtained during this study will be strictly kept strictly confidential. Only members of the study team will have access to information. You can with draw from the study any time without affecting your present or future medical care at the hospital.

After the study the data will be analyzed, the results and the explanation of its implications will be published for everyone's information. The identity of the participants will not be revealed.

All study related queries and problems if any should be communicated to Dr.Srinivas, Registrar, Department of urology, CMC, Vellore, Tamil Nadu.

Telephone – 0416 2282111

INFORMED CONSENT

Study Title: PROSPECTIVE ANALYSIS OF VOIDED AND BARBOTAGE URINE CYTOLOGY IN THE ROUTINE FOLLOW UP OF NON-MUSCLE INVASIVE TRANSITIONAL CELL CARCINOMA OF BLADDER

Study Number:
Subject's Initials: _____ Subject's Name: _____
Date of Birth / Age:_____
Please initial box
(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:_____
Date: _____/_____/_____
Signatory's Name: _____

Signature of the Investigator: _____
Date: _____/_____/_____
Study Investigator's Name: _____

Signature of the Witness: _____
Date:_____/_____/_____
Name of the Witness: _____

PROFORMA

Name:
Age:
Sex:
Hospital number:
Address:
Phone number:
Date of first resection:
Histopathology:

First biopsy: Lesion
pT stage
Grade

Immediate post-op intravesical chemotherapy:

Induction/maintenance BCG:

Number of recurrence:

Follow up since(months):

Investigations during the study:

Biochemistry: Urine microscopy Manual:
Urine culture and sensitivity:
Serum creatinine:

IVU if done during the study:
USG if done during the study:
CT if done during the study:

Cytology;
1. Voided urine cytology
2. Barbotage urine cytology

Cystoscopy findings:
1. Anatomy of urethra and bladder
2. Tumour – number
Size
Sessile/papillary/evidence of CIS

Histopathology of the recurrent tumour:
Lesion
pT stage
Grade

sno.	Name	Hosp.No.	Age in yrs	Sex	year of diagnosis primary tumor	primary tumor characteristics	single	multiple	CIS
1	sadan chakrabarty	590216d	64	1	30.4.09	pap.2x3.rt.lat	1	0	0
2	sadan chakravarthy	590216d	65	1	30.4.09	pap.2x3.rt.lat	1	0	0
3	atul chandra maity	533379d	58	1	10.9.09	pap0.5x0.5lat.dome	0	1	0
4	atul chandr maity	533379d	57	1	2005	papillary	0	1	0
5	pradip das	458110d	44	1	2.07.09	sessile.1x1 post wall	1	0	1
6	pradip das	458110d	44	1	2.07.09	preop cytology +	1	0	
7	budhan kahar	930779b	55	1	2000	papillary 2x2.post wall	1	0	0
8	netai das	551785d	58	1	may.07	papillary	1	0	1
9	netai das	551785d	58	1	may.07	papillary	1	0	1
10	tharmaraj	946591c	63	1	9.11.07	papillary	1	0	0
11	namita dangar	520088d	27	0	20.08.09	papillary	1	0	0
12	hari pada sarkar	469775c	60	1	28.5.04	papillary	1	0	1
13	afzal	416439d	31	1	17.3.09	papillary	1	0	1
14	arun kumar sarkar	605959d	51	1	24.12.09	pap.4x3.rt.u.o	1	0	0
15	Md.Farooque sahab	404669d	61	1	18.2.09	pap2x2.lt.lat.ant	0	1	0
16	uttam	801420c	54	1	6.5.06	pap.1x1.rt.u.o	1	0	0
17	shiv nath prasad	144365d	68	1	13.2.08	papillary,postwall,dome	0	1	0
18	shiv nath prasad	144365d	68	1	13.2.08	papillary,postwall,dome	0	1	0
19	gargee hazra	541317d	39	0	23.9.09	papillary2x2,postwall	1	0	0
20	gargee hazra	541317d	39	0	23.9.09	papillary2x2,postwall	1	0	0
21	sushil kumar singh	636053c	44	1	20.5.05	pap.3x3.rt.lat	1	0	0
22	arokia das	252247d	60	1	17.12.08	papillary	0	1	0
23	arokyadas	252247d	41	1	16.12.08	pap.sesile.1.5x1..5rt.lat	0	1	0
24	arokyadas	252247d	62	1	16.12.08	pap.sesile.1.5x1..5rt.lat	0	1	0
25	sisir mukerjee	527627d	56	1	1.9.09	pap.3x3.rt.lat.post	0	1	0
26	shambu nath prasad	144365d	56	1	12.12.07	pap.2x1.5.rt.u.o	1	0	0
27	shambu nath prasad	144365d	56	1	12.12.07	pap.2x1.5.rt.u.o	1	0	0
28	Md.farooque sahab	404669d	62	1	18.2 09	papillary,left lat.wall.ant wall.2x2cms	0	1	0
29	ramalingam	394876d	41	1	16.2.09	papillary4x3 rt.lat wall	1	0	0
30	ramalingam	394876d	41	1	16.2.09	papillary4x3 rt.lat wall	1	0	0
31	tarun kumar banerjee	947216c	58	1	21.12.06	pap.0.2x0.5.dome.rtt.u.o	0	1	0
32	abdul aziz	627109d	60	1	21.12.06	outside	0	1	0
33	moshraf ali	747464c	54	1	2.1.06	pap.3x3.lt.lat	1	0	0
34	natarajan	252545d	77	1	13.6.08	papillary,0.5x2,post,dome	0	1	0
35	ramchandra prasad singh	762204c	69	1	17.1.06	scar tsissue lat wall	1	0	0
36	sujit samada	399701d	39	1	10.2.09	papillary,3x2,rt.lat wall	1	0	0

sno.	Name	Hosp.No.	Age in yrs	Sex	year of diagnosis primary tumor	primary tumor characteristics	single	multiple	CIS
37	abdul khalaque	620801d	76	1	apr.2009	papillary,3x2,rt.lat wall	1	0	0
38	kumar.t	486999b	58	1	26.3.07	papillary 0.8,trigone	1	0	0
39	gadadhar mondal	634492c	59	1	23.10.09	excision with blader cuff on 23.10.09	1	0	1
40	kumar	486999b	59	1	2001	pap1x1.post	0	1	0
41	kumar	486999b	59	1	2001	pap1x1.post	0	1	0
42	mriganka shankar giri	263996d	62	1	30.6.08	pap.2x0.5.dome.ant	0	1	0
43	md hashim	627739d	56	1	30.12.09	pap.2x2.rt.lat	1	0	0
44	haripada dasguta	759418b	77	1	10.9.02	pap.0.2x0.2.rt.u.o.post	0	1	0
45	haripada dasguta	759418b	77	1	10.9.02	pap.0.2x0.2.rt.u.o.post	0	1	0
46	kajal dey	699045c	49	0	20.9.05	papillary 2x2 dome.multiple recirrence	1	0	0
47	tarun kumar banerjee	947216c	60	1	22.12.06	pappilary2x2	1	0	0
48	khirod kumar mandal	274699d	43	1	28.7.08	sessile.3x2 above rt.u.o	1	0	0
49	kanakamma	502204b	57	0	2000	sessile.3x2 above rt.u.o	0	1	0
50	madhu sudhan roy	403199c	55	1	20.9.05	pap.0.7.0.3.dome	1	0	0
51	naba kumar goswami	913594b	45	1	30.6.04	pap.1x1.5.lt.u..o	1	0	0
52	gowrammal	599400c	60	0	10.3.2005	papilary1.5x1.postwall	1	0	0
53	quershi	385279d	72	1	10.2.09	papillaary3x3.rt.lat wall	1	0	0
54	kankkamma	502204b	55	0	27.11.00	pap.0.7.0.3.dome	1	0	0
55	ashok kumar yadav	766767c	38	1	8.2.06	pap.1x1.5.lt.u..o	1	0	0
56	moshraf ali	747464c	53	1	14.12.06	pap.3x3.lt.lat	1	0	0
57	musharraf hussain talukdar	506795d	63	1	20.4.08	pap.3x2.dome.rt.lat	0	1	0
58	musharraf hussain talukdar	506795d	63	1	20.4.08	pap.3x2.dome.rt.lat	0	1	0
59	bhulu mitra	964496b	54	1	21.4.06	papillary 1x0.5.above rt.u.o	1	0	0
60	celina ranee	410965d	64	0	26.2..09	papillary 2x1 lt.lat wal	1	0	0
61	md.saifuddin	334080c	43	1	24.7.03	papillary 1x2.dome.postwall	0	1	0
62	gowrammal	599400c	65	0	7.1.05	pap.1.5x1.rt.lat	1	0	0
63	narayan pillai	771540c	67	1	17.2.03	pap.3x3.ant.1x1.lt.lat	0	1	0
64	narayan pillai	771540c	67	1	17.2.03	pap.3x3.ant.1x1.lt.lat	0	1	0
65	narayan pillai	771540c	67	1	17.2.03	pap.3x3.ant.1x1.lt.lat	0	1	0
66	md.saifuddin	334080c	55	1	24.7.03	pap.2x3.dome	0	1	0
67	niranjan biswas	123479d	69	1	18.3.10	pap.2x2.post	1	0	0
68	niranjan biswas	123479d	69	1	18.3.10	pap.2x2.post	1	0	0
69	niranjan biswas	123479d	69	1	18.3.10	pap.2x2.post	1	0	0
70	krishn pada biswas	581563d	55	1	16.11.09	papillary 0.5x0.5.trigone	1	0	0
71	krishn pada biswas	581563d	55	1	16.11.09	papillary 0.5x0.5.trigone	1	0	0
72	krishn pada biswas	581563d	55	1	16.11.09	papillary 0.5x0.5.trigone	1	0	0

sno.	Name	Hosp.No.	Age in yrs	Sex	year of diagnosis primary tumor	primary tumor characteristics	single	multiple	CIS
73	sarojamma	565328d	65	0	13.11.09	papillaary3x3.lt.lat wall	1	0	0
74	sarojamma	565328d	65	0	13.11.09	papillaary3x3.lt.lat wall	1	0	0
75	gad dhar roy	430124d	67	1	24.3.09	sess.2x2.rt.lat	1	0	0
76	gad dhar roy	430124d	55	1	24.3.09	sess.2x2.rt.lat	1	0	0
77	naarayan pillai	7715540c	67	1	17.2.06	pappilary,lat ant,wall,circumferentially neck	0	1	0
78	naarayan pillai	7715540c	67	1	17.2.06	pappilary,lat ant,wall,circumferentially neck	0	1	0
79	pollu yasodamma	500284d	55	0	30.09.09	papillary1x0.5.lt.lat.post wall	0	1	0
80	gadadhar roy	430124d	54	1	24.3.09	sessile2x2.lt.lat.wall	1	0	0
81	gadadhar roy	430124d	54	1	24.3.09	sessile2x2.lt.lat.wall	1	0	0
82	shaji john	629147c	36	1	13.5.05	pap.1x2.rt.lat	1	0	0
83	ramanathan	411797c	81	1	21.9.05	pap.3x3	1	0	0
84	ram prabodh singh	050203d	53	1	22.6.07	papillary1x1 lt.latwall	0	1	0
85	ram prabodh singh	050203d	53	1	22.6.07	papillary1x1 lt.latwall	0	1	0
86	vengojammal	949763c	60	0	3.4.07	papillary.2x3.rt.lat wall	0	1	0
87	vengojammal	949763c	60	0	3.4.07	papillary.2x3.rt.lat wall	0	1	0
88	brundaban mohanty	865948c	49	1	2.8.06	papilary.1x3.rt.lat	0	1	0
89	amar ghosh	449729d	55	1	1.5.09	pap.multiple thro.out UB.turt.twice	0	1	0
90	amar ghosh	449729d	55	1	1.5.09	pap.multiple thro.out UB.turt.twice	0	1	0
91	amar ghosh	449729d	56	1	1.5.09	papillary thr out UB	0	1	0
92	amar ghosh	449729d	56	1	1.5.09	papillary thr out UB	0	1	0
93	uday kumar 34	865389c	34	1	7.8.06	papillary	1	0	0
94	uday kumar 34	865389c	34	1	7.8.06	papillary	1	0	0
95	uday kumar 34	865389c	34	1	7.8.06	papillary	1	0	0
96	dibakar das	515811d	37	1	7.8.09	pap.0.5x0.5.lt.lat	0	1	1
97	dibakar das	515811d	37	1	7.8.09	pap.0.5x0.5.lt.lat	0	1	1
98	dibakar das	515811d	37	1	7.8.09	pap.0.5x0.5.lt.lat	0	1	1
99	muthu	576366d	68	1	14.12.09	pap.2x3.rt.lat	1	0	0
100	muthu	576366d	68	1	14.12.09	pap.2x3.rt.lat	1	0	0
101	paltu sardar	190882d	49	1	26.2.08	pap.2x3.rt.lat	1	0	0
102	ashok kumar tripathy	271382d	49	1	26.2.08	pap.2x2.rt.u.o	1	0	0
103	ashok kumar tripathy	271382d	49	1	26.2.08	pap.2x2.rt.u.o	1	0	0
104	ashok kumar tripathy	271382d	49	1	14.5.10	pap.2x2.rt.u.o	1	0	0
105	ismail	653399d	64	1	14.5.10	mul.pap.sessile.thr.out u.b	0	1	1
106	sivanthi adithan	211649d	62	1	1.4.08	pap.6x6.dome	1	0	1
107	sambu nath datta	687443d	49	1	11.5.10	pap.2.5.2.rt.lat	1	0	0
108	sambu nath datta	687443d	49	1	11.5.10	pap.2.5.2.rt.lat	1	0	0

sno.	Name	Hosp.No.	Age in yrs	Sex	year of diagnosis primary tumor	primary tumor characteristics	single	multiple	CIS
109	rabindranath dhar	717716d	42	1	2009	pap.2.5.2.rt.lat	1	0	0
110	jesudas jabamani	048635d	66	1	3.7.07	pap.1x1.5.rt.lat	1	0	0
111	jesudas jabamani	048635d	66	1	3.7.07	pap.1x1.5.rt.lat	1	0	0
112	jesudas jabamani	048635d	66	1	3.7.07	pap.1x1.5.rt.lat	1	0	0
113	kasinath das	480873d	46	1	may.09	papillary 0.5x0.5.lt.lat	1	0	0
114	dilip saha	598805d	49	1	28.12.09	pap.1.5.2.rt.lat	1	0	0
115	asim banerjee	718667d	47	1	2.7.10	ses.4x3.dome.lt.lat	1	0	1
116	gowri shankar gayal	569640c	55	1	2.7.10	papillary 0.5x0.5.lt.lat	1	0	0
117	joseph athisayam	469469c	70	1	12.5.04	papillary 0.5x0.5.lt.lat	1	0	0
118	subramaniam	690289d	49	1	14.5.10	pap.3x3.lt.lat	1	0	0
119	subramaniam	690289d	49	1	14.5.10	pap.3x3.lt.lat	1	0	0
120	pratima das	805929d	47	0	2.7.10	pap.1x0.5.ant &rt.lat	0	1	0
121	mridul chandr roy	776616c	24	1	1.3.06	pap2x1.5.rt.lat	1	0	0
122	biplab ray	419019c	62	1	9.2.04	pap.4x2.ant.wall	1	0	0
123	durai pandi	427956d	48	1	19.3.09	pap.1x0.5.ant &rt.lat	0	1	0
124	durai pandi	427956d	48	1	2.7.10	pap.1x0.5.ant &rt.lat	0	1	0
125	durai pandi	427956d	48		2.7.10	pap.1x0.5.ant &rt.lat	0	1	0
126	amulya chandra mandal	569750d	64	1	17.11.2009	pap.1x1.5.lt.u..o	1	0	0
127	amulya chandra mandal	569750d	64	1	17.11.2009	pap.1x1.5.lt.u..o	1	0	0
128	amulya chandra mandal	569750d	64	1	17.11.2009	pap.1x1.5.lt.u..o	1	0	0
129	sunil kumar panda	198145d	36	1	26.3.08	papillary3x2.above rt.ur.orifice	1	0	0
130	ram nandan mandal	939089c	46	1	28.11.06	rt.lat.outside	1	0	0
131	niresh kundu	111159c	36	1	2003	?pap.3x3.rt.lat	1	0	0
132	gandhi	918446c	58	1	24.11.09	papillary 3x3 lt.latwall	1	0	0
133	sukumar duta	399638c	67	1	18.11.08	pap.2x3.rt.lat	1	0	0
134	sukumar duta	399638c	67	1	18.11.08	pap.2x3.rt.lat	1	0	0
135	laxmi	494365c	58	0	5.6.09	pap.4 tumor.4x4.rt.lat+1x1	0	1	0
136	laxmi	494365c	58	0	15.6.09	pap.4 tumor.4x4.rt.lat+1x1	0	1	0
137	laxmi	494365c	58	0	5.6.09	pap.4 tumor.4x4.rt.lat+1x1	0	1	0
138	joseph	423031c	74	1	13.2.04	pap.4x2.rt.lat	0	0	0
139	manickiam	447798d	40	1	6.5.09	pap.5x4.lt.lat.uo.+wall	1	0	0
140	jamaluudin	626310d	64	1	2.2.10	papilary3x3,rt.lat wall	1	0	0
141	sk.jamaluddin	626310d	63	1	2.2.10	papilary3x3,rt.lat wall	1	0	0
142	sk.jamaluddin	140501a	44	1	26.11.07	papilary3x3,rt.lat wall	1	0	0
143	sk.jamaluddin	140501a	44	1	26.11.07	papilary3x3,rt.lat wall	1	0	0
144	jitendra kumar tak	183938d	56	1	19.2.08	sessile.1x1 post wall	1	0	0

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145	shashanka sekar mandal	656861d	60	1	29.3.10	pap.2x3.rt.lat	1	0	0
146	madhusudhan biswas	014223d	62	1	1.5.07	pap.3x3.lt.lat	1	0	0
147	mathew	647862d	59	1	15.1.10	pap.3x3.lt.lat	1	0	1
148	ajit kumar bera	309277d	73	1	8.09.08	sessile.1x1 post wall	1	0	0
149	panniyapan	806297b	62	1	2003	pap.multiple	0	1	0
150	gour gopal jana	621204c	45	1	0.11.04	pap.2x3.rt.lat	1	0	0
151	subramaniam	368249d	68	1	28.12 .09	papillary.3x3.0.5x0.5.dome .ant.lat wall	0	1	0
152	subramaniam	368249d	68	1	28.12 .09	papillary.3x3.0.5x0.5.dome .ant.lat wall	0	1	0
153	kirid kumar mandal	274699d	44	1	28.1.08	pap3x2.r.lat	1	0	0
154	santa saha	607173d	43	1	28.12 .09	pap.4x4.	1	0	0
155	santa saha	607173d	43	1	28.12.09	pap.4x4.	1	0	0
156	jaganath maity	169611b	63	1	?2003	sessile.1x1 post wall	1	0	0
157	kali pada patra	656425d	73	1	27.3.10	pap.multiple	0	1	0
158	sankar dutta	746942d	55	1	23.6.10	pap.2x1.rt.lat	1	0	0
159	sankar dutta	746942d	55	1	23.6.10	pap.2x1.rt.lat	1	0	0
160	pradip das	458110d		1	2.07.09	sessile.1x1 post wall	1	0	1
161	pradip das	458110d	44	1	2.07.09	sessile.1x1 post wall	1	0	1
162	rajesh arora	118427c	64	1	24.1.02	pap.multiple 0.2	0	1	0
163	subhas chatrejee	333737c	61	1	8.1.07	pap.rt.lt.ant.wall	0	1	0
164	samir saha	722194d	46	1	24.6.10	pap.3x2.lt.lat	1	0	0
165	mohamed jainul	645019d	50	1	24.3.06	sess.0.5x0.5.post wall	1	0	0
166	mohamed jainul	645019d	50	1	24.3.06	sess.0.5x0.5.post wall	1	0	0
167	pushpa dey	199052d	60	0	13.3.08	pap.0.5x0.5rt.u.o	1	0	0
168	atul chandr maity	533379d	58	1	2005	pap.2x3,1x1.lt.u.o	0	1	0
169	nakul mitr	430764c	32	1	26.2.04	pap.5x3.rt.lat	1	0	0
170	kali prasad saha	772692d	62	1	24.9.10	pap.0.5x0.5rt.u.o	1	0	0
171	ganesan	754122d	54	1	13.7.04	pap.0.5x0.5rt.u.o	1	0	0
172	jayanthi basak	620668d	30	0	31.1.10	papillary2x2,postwall,lat wall	0	1	0
173	ismail	705947d	63	1	1.6.10	pap.1.5x1.rt.lat	1	0	0
174	ismail	705947d		1	1.6.10	pap.1.5x1.rt.lat	1	0	0
175	sanath kumar mukerjee	728158c	72	1	1711.05	pap.2.5x2.5.rt.u.o	1	0	0
176	sija grewal	523311d	34	0	26.8.09	pap.0.5x0.5rt.u.o	1	0	0
177	purna chandra madhani	720085d	51	1	7.7.10	pap.2x3,1x1.lt.u.o	0	1	0
178	ashok kumar ray	946952b	59	1	1999	pap.1.5x1.rt.lat	1	0	0
179	anukul das	753565b	60	1	6.5.1999.	4tumor.2x2.1x2.3x2	0	1	0
180	sudhangshu kumar roy	642739d	63	1	7.3.10	pap.2x3,rt..u.o	1	0	0

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181	dharmaraj	946591c	66	1	9.11.07	pap.cis.3x2.rt.lt.post	0	1	1
182	naresh prasad gupta	517246b	63	1	2003	pap.cis.3x2.rt.lt.post	0	1	1
183	dilip rambabu	348575b	53	1	27.3.07	pap.3x3.lt.u.o	1	0	0
184	shardammal	113882d	76	0	3.1.08	pap.0.5x0.5rt.lat	0	1	0
185	muni krishna	692124d	70	1	20.5.10	pap.3x2.trigone.post	0	1	0
186	chitranjan gowsami	377537d	63	1	23.12.08	papillary3x3postwall	1	0	1
187	lalitha alexander	736811d	75	0	16.8.07	sess.0.3x0.3.post	0	1	0
188	surendra nath chuan	264254c	62	1	2003	pap.sesile.1.5x1..5rt.lat	0	1	0
189	md.atul.haque	683875d	69	1	24.5.10	pap.1.5x1.5.rt.lat	1	0	0
190	niranjan biswas	123479d	69	1	18.3.10	pap.2x2.post	1	0	0
191	suniti ghosh	473294d	52	0	11.6.09	pap.1.5x1.rt.lat	1	0	0
192	anil chandra ray	337187d	59	1	18.11.08	pap.sessile thro.out.UB.resected twice	0	0	0
193	anil chandra ray	337187d	59	1	18.11.08	pap.sessile thro.out.UB.resected twice	0	0	0
194	saheb ali	141024d	64	1	20.11.07	sess4x3.lt.lat	1	0	0
195	nilakanta das	319349d	49	1	25.09.08	pap.sessile thro.out.UB.resected twice	0	0	0
196	katahu ram	700672d	73	1	28.5.10	pap4x4.lt.lat.post	0	1	0
197	dilwar rehman	561363d	66	1	23.10.09	pappilary & sessile,rt.lat,post wall,neck	0	1	0
198	nimai hansda	714359d	48	1	18.6.10	pap2x2.lt.lat	1	0	0
199	md.sahajahan	819594d	52	1	1.22003	pap.2x3	1	0	0
200	bijoy patra	218678d	56	1	20.8.07	pap.4x3.lt.lat.post	1	0	0
201	nani gopal chowdhary	310527d	62	1	24.2.09	papillary.1.5x1.5.rt.u.o.lat.wall	0	1	0
202	sauktiya kamin	483563d	50	1	20.08.10	pap2x2.lt.lat	1	0	0
203	hari pada das gupta	759418b	57	1	19.12.06	pappilary	0	1	0
204	ramesh chandra kalita	377384d	57	1	26.12.08	pap.3x3.lt.lat	0	1	0
205	madhu sudhan roy	403199c	71	1	26.12.08	pappilary	0	1	0
206	ramalingam	394876d	42	1	19.12.06	sess4x3.lt.lat	1	0	0
207	sivanthi adithan	211649d	63	1	3.4.08	pap.6x6.dome.biman.pal	1	0	1
208	md.fazlul kabir	710687d	52	1	13.3.10	?pap.3x2.rt.lat	1	0	0
209	basudeb adhikary	755613d	52	1	20.08.10	pap2x2.lt.lat	1	0	0
210	basudeb adhikary	755613d	52	1	20.08.10	pap2x2.lt.lat	1	0	0
211	asim bhandopadhyay	718667d	48	1	2.7.10	sess4x3.lt.lat	1	0	0
212	samir battacharya	773306d	52	1	7.9.10	pap2x2 lt.lat	1	0	0
213	kamal kanti ghosh	946544c	68	1	19.12.06	pappilary	0	1	0
214	Md.Azimuddin Ansari	617803d	64	1	21.1.10	pap.2x3.rt.u.o	1	0	0
215	krishnaiah	668861d	54	1	18.5.10.	pap5x5.lt.lat.ant	0	1	0
216	jolly mathew	310866d	45	0	26.8.08	pap.1.5x1.rt.u.o.post	0	1	0

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217	nedunchezian	140501a	42	1	20.11.07	pap3x1.rt.lat	1	0	0
218	devaraj	978070c	44	1	10 .10.07	pap3x1.rt.lat	1	0	0
219	phatik banerjee	949322b	54	1	10.9.09	pap1x1.dome.lt.lat	0	1	0
220	madhab chandra bhandary	421170d	55	1	10.12.08	pap3x1.lt.lat	0	1	0
221	murugesan	684824d	59	1	11.4.10,	pap.2x2.dome.lt.lat.post.neck	0	1	0
222	bijay kumar sarkar	743720c	51	1	2003	pap.1x0.5.ant &rt.lat	0	1	0
223	pradeep kumar chowdhary	233888d	52	1	12.5.08	pap.2x3.rt.lay	1	0	0
224	mukhlal prasad gupta	053077d	64	1	5.7.07	pap.2x2.1x1.rt & lt.lat	0	1	0
225	mathew	647862d	53	1	12.1.10	pap.2x3.rt.&.lt.lat	0	1	1
226	sasanka sekar mandal	656861d	35	1	29.3.10	pap.3x2.5.neck	1	0	0
227	shankar kumar pal	434619d	64	1	6.4.09	pap.2x2.1x1.rt & lt.lat	0	1	0
228	bhubaneswar roy	746364d	35	1	2008	pap.2x2.1x1.rt & lt.lat	0	1	0
229	sudangshu kumar roy	642739d	63	1	12.3.10	pap.2x2.lt.u.o	1	0	0
230	basudeb dahikary	755613d	52	1	20.8.10	pap.2x2.lt.lat	1	0	0
231	anukul das	753565b	60	1	6.5.10	pap.3x2.rt.lat	1	0	0
232	quershi	385279d	72	1	19.12.06	pap.lt.alt&ant.neck	0	1	0
233	quershi	385279d	72	1	19.12.06	pap.lt.alt&ant.neck	0	1	0
234	madhab chandra bhandary	421170d	56	1	10.12.08	sessile 2x2.lt.lat wall	1	0	0
235	md.sharifulislam	361976d	46	1	28.11.08	pap.1x2.rt.lat	1	0	0
236	nirmal kumar jain	143897c	56	1	1.4.03	pap.lt.alt&ant.neck	0	1	0
237	sukumar duta	356886d	59	1	18.11.08	pap.3x3.lt.lat	0	1	0
238	narayan chandra das	317901b	60	1	2001	pappilary & sessile,rt.lat,post wall,neck	0	1	0
239	dilip kumar mondal	757899c	50	1	10.3.06	pap2.5x2.5.above rt.u.o	1	0	0
240	asit das	748175c	47	1	23.12.05	pap.1x2.rt.lat.narrow stalk	1	0	0
241	abrar ali	184646d	58	1	19.2.08	pap.1x2.rt.u.o	1	0	0
242	nitya ranjan mondal	246628C	57	1	1998	4papgrowth.4x5	1	0	0
243	nitya ranjan mondal	246628C	57	1	1998	4papgrowth.4x5	1	0	0
244	sankar kumar pal	434619d	63	1	6.4.09	pap.1x2.rt.lat	1	0	0
245	krishnaiah	668861d	56	1	18.5.10	pap.rt.lat+ant.5x4	1	0	0
246	partha pratim ghosal	047819d	50	1	29.6.07	pap.2x2 lt.lat	1	0	0
247	dilwar rehman	561363d	66	1	23.10.09	pappilary & sessile,rt.lat,post wall,neck	0	1	0
248	vasantha kumari	148029d	35	0	23.2.10	pap.2x2 lt.u.o	1	0	0
249	narayan chandra ganai	128486d	45	1	2.7.10	pap.3x2.rt.lat	1	0	0
250	sushil kumar singh	636053c	45	1	20.5.05	pap.rt.lat+ant.5x4	1	0	0

sno.	primary tumor stage/grade	intravesical chemotherapy	BCG	Date of follow up	recurrent tumor stage/grade	voided urine cytology	Barbotage urine cytology	cystoscopy	UTI present study
1	tag2	1	0	30.11.09	0	0	0	0	0
2	tag2	1	0	24.9.10	0	0	0	0	0
3	tag2	1	0	21.12.09	0	2	0	0	0
4	tag2	1	1	18.12.09	1	0	0	0	0
5	t1g3	0	1	18.05.10	0	0	0	0	0
6	t1g3	0	1	27.06.09	tig2	0	0	1	0
7	tag2	1	0	16.8.09	tag2	1	1	1	0
8	tag2	0	0	31.12.09	0	0	0	0	0
9	tag2	0	0	17.6.10	0	0	0	0	0
10	t1g3	0	1	14.12.09	0	0	0	0	0
11	tag2	0	0	26.12.09	0	0	0	0	0
12	t1g2	0	0	29.12.09	0	0	0	0	0
13	tag2	0	0	30.12.09	0	0	0	0	0
14	t1g3	1	0	1.1.10	t1g3	1	1	1	0
15	tag2	1	0	12.1.10	tag2	1	1	1	0
16	t1g2	1	0	13.1.10	0	0	1	0	1
17	t1g3	1	1	13.1.10:	0	1	1	0	1
18	t1g3	1	1	18.9.10	0	0	0	0	0
19	tag2	1	0	13.1.10	0	0	0	0	0
20	tag2	1	0	16.8.10	0	0	2	0	0
21	t1g3	1	1	21.1.10	0	0	0	0	0
22	tag2	1	0	13.1.10	tag2	0	0	1	0
23	tag2	1	0	12.7.10	0	0	0	0	0
24	tag2	1	0	7.10.10	0	0	0	0	0
25	t1g3	1	0	27.1.10	0	1	2	0	0
26	t1g3	1	1	14.1.10	tig2	1	0	1	0
27	t1g3	1	0	16.9.10	0	0	0	0	0
28	tag2	1	0	12.01.10	tag2	1	1	1	0
29	tag2	1	0	15.1.10	0	0	0	0	0
30	tag2	1	0	30.4.10	0	0	0	0	0
31	tag2	1	0	18.2.10	0	0	0	0	0
32	t1g1	1	0	29.1.10	0	0	0	0	0
33	t1g2	1	1	8.2.10	0	0	0	0	0
34	t1g3	1	1	21.1.10	0	0	0	0	0
35	t1g3	1	1	28.1.10	0	0	0	0	0
36	tag2	1	0	28.1.10	0	0	0	0	0

sno.	primary tumor stage/grade	intravesical chemotherapy	BCG	Date of follow up	recurrent tumor stage/grade	voided urine cytology	Barbotage urine cytology	cystoscopy	UTI present study
37	tag2	1	0	1.2.10	0	1	1	0	0
38	tag2	0	0	5.2.10	0	0	0	0	0
39	tig3 cis	0	1	8.2.10	cis	1	1	1	1
40	tag1	1	0	14.1.11	0	0	0	0	0
41	tag1	1	0	5.2.10	0	0	0	0	0
42	tag2	1	0	16.4.10	0	0	0	0	0
43	t1g2	1	0	1.2.10	0	1	1	1	0
44	tag2	1	0	22.3.10	tag2	1	1	1	0
45	tag2	1	0	26.11.10	tag2	0	1	1	0
46	t1g2	1	1	15.2.10	0	0	0	0	0
47	tag2	0	1	18.2.10	0	0	0	0	1
48	t1g3	1	1	19.2.10	0	0	0	0	1
49	tig3	0	1	23.2.10	0	0	0	0	1
50	tag2	1	0	24.2.10	0	0	0	0	0
51	t1g2	0	0	24.2.10	0	0	0	0	0
52	t1g2	0	0	25.2.10	tag2	0	1	1	0
53	tag2	0	0	18.2.10	0	0	1	0	0
54	t1g2	1	0	17.2.10	0	2	0	0	0
55	t1g2	1	0	8.5.10	0	0	0	0	0
56	t1g2	1	1	8.2.10	0	0	0	0	0
57	tag1	1	0	1.2.10	0	0	0	0	0
58	tag1	1	0	21.8.10	0	0	1	0	0
59	t1g2	1	0	25.2.10	tag2	0	1	1	0
60	tag2	1	0	26.2.10	0	0	0	0	0
61	tag3	1	0	4.3.10	0	0	0	0	0
62	t1g2	1	0	3.3.10	tag2	0	1	1	0
63	t1g2	0	0	11.1.11	t1g3	1	0	1	0
64	t1g2	0	0	8.7.10	0	1	1	0	0
65	t1g2	1	1	18.3.10	0	0	0	0	0
66	t1g3	1	0	4.3.10	0	0	0	0	0
67	tag2	1	0	13.1.11	0	0	0	0	0
68	tag2	1	0	24.6.10	0	0	1	0	0
69	tag2	1	0	18.3.10	tag2	0	0	1	0
70	t1g2	1	0	4.3.10	0	0	0	0	0
71	t1g2	1	0	18.6.10.	0	0	0	0	0
72	t1g2	1	0	22.11.10	0	0	0	0	0

sno.	primary tumor stage/grade	intravesical chemotherapy	BCG	Date of follow up	recurrent tumor stage/grade	voided urine cytology	Barbotage urine cytology	cystoscopy	UTI present study
73	t1g2	1	1	1.3.10	0	0	0	0	0
74	tag2	0	0	17.6.10	0	0	0	0	0
75	t1g3	0	1	9.9.10	0	0	0	0	0
76	t1g3	1	1	8.3.10	0	0	0	0	0
77	t1g2	1	1	18.3.10	0	0	0	0	0
78	t1g2	1	0	8.7.10	0	1	0	0	0
79	t1g3	1	0	5.3.10	t1g3	1	0	1	1
80	t1g3	1	1	5.3.10	0	0	0	0	0
81	t1g3	1	1	9.9.10	0	0	0	0	0
82	t1g3	0	1	29.3.10	0	0	0	0	0
83	t1g2	0	0	29.3.10	0	0	0	0	1
84	t1g1	1	0	9.3.10	0	0	0	0	0
85	t1g1	1	0	17.8.10	0	0	0	0	0
86	t1g2	1	0	23.3.10	0	0	0	0	0
87	t1g2	1	0	22.10.10	0	0	0	0	0
88	tag2	1	0	23.3.10	0	0	0	0	0
89	t1g3	0	1	25.3.10	0	0	0	0	0
90	t1g3	0	1	24.6.10,	0	0	0	0	0
91	t1g3	1	1	29.11.10	chr cyst	0	0	1	0
92	t1g3	1	1	10.12.09	0	0	0	0	0
93	t1g2	0	0	25.3.10	0	0	0	0	0
94	t1g2	0	0	12.7.10,	0	0	0	0	0
95	t1g2	0	0	12.10.10	0	0	0	0	0
96	t1g3	0	1	26.3.10	0	1	0	0	0
97	t1g3	0	1	31.7.10	0	0	0	0	0
98	t1g3	0	1	7.12.10	0	0	0	0	0
99	t1g2	1	0	20.8.10	0	0	0	0	0
100	t1g2	1	0	20.3.10	0	0	0	0	0
101	t1g3	1	1	21.10.10	0	0	0	0	0
102	t1g3	1	1	12.1.11	t1g2	0	0	1	0
103	t1g3	1	1	18.9.10	0	0	0	0	0
104	t1g3	1	1	14.6.10	0	1	0	0	0
105	t1g3	0	1	15.6.10	bcg cystitis	1	0	1	0
106	t1g3	1	1	18.6.10	tig3	0	1	1	0
107	t1g3	1	1	22.6.10	0	0	1	0	0
108	t1g3	1	1	26.11.10	0	0	0	0	0

sno.	primary tumor stage/grade	intravesical chemotherapy	BCG	Date of follow up	recurrent tumor stage/grade	voided urine cytology	Barbotage urine cytology	cystoscopy	UTI present study
109	tag2	1	0	21.6.10	0	0	0	0	0
110	t1g3	1	1	24.6.10	0	2	0	0	0
111	t1g3	1	1	27.12.10	0	0	0	0	0
112	t1g3	1	1	10.1.11	0	0	0	0	0
113	t1g3	1	1	20.6.10	tag2	0	1	1	0
114	tag2	1	0	29.6.10	0	0	0	0	0
115	cis	0	1	23.112.10	0	0	0	0	0
116	t1g2	1	0	14.6.10	0	0	0	0	0
117	t1g2	0	0	17.6.10	0	0	0	0	0
118	t1g3	1	bcg	2.7.10.	chr cyst	0	1	1	0
119	t1g3	1	1	8.10.10	0	0	0	0	0
120	t1g2	1	0	21.10.10	0	0	0	0	0
121	tag2	1	0	9.7.10	0	0	0	0	0
122	t1g2	0	1	9.7.10	0	0	0	0	0
123	t1g3	1	1	12.7.10	0	0	0	0	0
124	t1g3	1	1	7.10.10	0	0	0	0	0
125	t1g3	1	1	7.1.11	0	0	0	0	0
126	tag2	1	0	16.3.10	0	0	0	0	0
127	tag2	1	0	29.11.10	0	0	0	0	0
128	tag2	1	0	24.6.10	0	1	1	0	0
129	t1g3	1	1	24.6.10	0	0	0	0	0
130	tag2	0	0	29.6.10	0	0	0	0	0
131	t1g2	1	0	5.7.10	0	0	0	0	0
132	t1g2	1	0	6.7.10	0	0	0	0	0
133	t1g2	1	0	8.7.10	0	0	0	0	0
134	t1g2	1	0	13.12.10	0	0	0	0	0
135	tig3	1	1	10.4.10	0	0	0	0	0
136	t1g3	1	1	15.7.10	chr cyst	0	0	1	0
137	t1g3	1	1	11.10.10	0	0	0	0	0
138	t1g2	1	0	21.10.10	0	0	0	0	0
139	t1g2-3	1	1	19.7.10	0	0	0	0	0
140	tag2	1	0	4.11.10	0	0	0	0	0
141	tag2	1	0	19.7.10	0	0	2	0	0
142	t1g3	1	1	29.1.08	0	0	0	0	0
143	t1g3	1	1	20.7.10	0	0	0	0	0
144	t1g2	0	0	20.7.10	0	0	0	0	0

sno.	primary tumor stage/grade	intravesical chemotherapy	BCG	Date of follow up	recurrent tumor stage/grade	voided urine cytology	Barbotage urine cytology	cystoscopy	UTI present study
145	tag2	1	0	21.7.10	0	0	0	0	0
146	tag2	1	0	22.7.10	t1g2	0	0	1	0
147	t1g3	0	1	22.7.10	bcg cystitis	0	0	1	0
148	tag2	0	0	26.7.10	0	1	0	0	0
149	?tag2	0	0	27.7.10	0	0	0	0	0
150	tag2	1	0	29.7.10	0	0	0	0	0
151	tag3	1	0	30.7.10	0	0	0	0	0
152	tag3	1	0	17.12.10	0	0	0	0	0
153	t1g3	1	1	31.7.10	0	0	0	0	0
154	t1g2	1	0	5.8.10	0	0	0	0	0
155	t1g2	1	0	5.4.10	0	0	0	0	0
156	tag2	0	0	6.8.10	0	0	0	0	0
157	t1g2	1	0	9.8.10	0	0	0	0	0
158	tag2	1	0	15.11.10	0	0	0	0	0
159	tag2	1	0	9.8.10	0	0	0	0	0
160	t1g3	1	1	19.8.10	0	0	0	0	0
161	t1g3	0	1	15.11.10	0	0	0	0	0
162	t1g2	1	0	24.8.10	0	0	0	0	0
163	t1g3	1	1	24.8.10	0	0	0	0	0
164	tag2	1	0	27.8.10	0	0	0	0	0
165	t1g2	1	1	26.3.10	t1g2	0	0	1	0
166	t1g2	1	1	28.8.10	0	0	0	0	0
167	t2g3	1	1	30.8.10	0	0	0	0	0
168	tag2	0	0	10.9.10	0	0	0	0	0
169	t1g2	1	0	10.9.10	0	0	0	0	0
170	tag1	1	0	27.12.10	0	0	0	0	0
171	tag2	1	0	14.9.10	chr cyst	0	0	1	0
172	tig3	1	1	20.9.10	0	0	0	0	0
173	tag2	1	0	16.12.10	0	0	0	0	0
174	tag2	0	0	16.9.10	0	0	0	0	0
175	t1g2	1	0	17.9.10	0	0	0	0	0
176	tag2	1	0	20.9.10	0	0	0	0	0
177	t1g2	1	0	21.9.10	chr cyst	0	0	1	0
178	tag2	1	0	18.5.07	tag2	0	0	1	0
179	t1g3	1	1	23.9.10	chr cyst	0	0	1	0
180	t1g3	1	1	23.9.10	t1g3	0	0	1	0

sno.	primary tumor stage/grade	intravesical chemotherapy	BCG	Date of follow up	recurrent tumor stage/grade	voided urine cytology	Barbotage urine cytology	cystoscopy	UTI present study
181	t1g3	1	1	27.9.10	0	0	0	0	0
182	t1g3	1	1	27.9.10	0	0	0	0	0
183	tag1	1	0	30.9.10	0	2	0	0	0
184	tag1	1	0	30.9.10	0	0	0	0	0
185	tag3cis	1	1	30.9.10	0	2	0	0	0
186	t1g3	1	1	9.4.10	0	0	0	0	1
187	t1g3	1	1	7.10.10	0	0	0	0	0
188	t1g2	1	0	11.10.10	t1g2	0	0	1	0
189	tag3	1	0	15.10.10	0	0	0	0	0
190	tag2	1	0	18.10.10	0	0	0	0	0
191	tag3	1	1	22.10.10	0	0	0	0	0
192	t1g3	0	1	28.10.10	0	0	0	0	0
193	t1g3	0	1	14.4.10	0	0	0	0	0
194	t1g3	1	1	29.10.10	0	0	0	0	0
195	t1g3	1	1	29.10.10	0	0	0	0	0
196	tag2	1	0	4.11.10	0	0	0	0	0
197	t1g3	0	1	8.11.10	0	0	0	0	0
198	tag2	1	0	10.11.10	0	0	0	0	0
199	t1g3	1	1	15.11.10	0	0	0	0	0
200	t1g3	1	1	15.11.10	0	0	0	0	0
201	tag2	1	0	22.11.10	tag21	0	0	1	0
202	tag2	1	0	25.11.10	0	0	0	0	0
203	tag2	0	0	25.11.10	0	0	0	1	0
204	tag2	1	0	31.3.10	tag2	0	1	1	0
205	tag2	0	0	6.12.10	0	0	0	0	0
206	tag2	1	0	7.12.10	0	0	0	0	0
207	t1g3	0	1	7.12.10	0	0	1	0	0
208	t1g3	1	1	9.6.10	t1g3	1	1	1	0
209	t1g3	1	1	16.12.10	chr cyst	1	0	1	0
210	t1g3	1	1	22.09.10	0	0	0	0	0
211	CIS	1	0	23.12.10	0	0	0	0	1
212	tag2	1	0	31.12.10	0	0	0	0	0
213	t1g3	1	1	19.4.10		0	0	0	
214	t1g3	1	0	13.10.10	t1g3	1	1	1	0
215	t1g2	1	0	1.3.8.10	0	0	0	0	0
216	tag2	1	1	10.8.10	0	0	0	0	0

sno.	primary tumor stage/grade	intravesical chemotherapy	BCG	Date of follow up	recurrent tumor stage/grade	voided urine cytology	Barbotage urine cytology	cystoscopy	UTI present study
217	t1g3	1	0	20.7.10	0	0	0	0	0
218	tag2	1	0	13.7.10	0	0	0	0	0
219	t1g2	1	0	8.6.10	0	0	0	0	0
220	tag2	1	0	16.7.10	0	0	0	0	0
221	t1g3	1	1	23.7.10	t1g3	0	0	1	0
222	tag2	1	0	22.7.10	tag2	0	0	1	0
223	t1g2	1	0	23.7.10	0	0	0	0	0
224	t1g2	1	0	22.7.10	0	0	0	0	0
225	t1g3	0	1	22.7.10	bcg cystitis	0	0	1	0
226	tag2	1	1	22.7.10	0	0	0	0	0
227	tag2	1	0	4.5.10	0	0	0	0	0
228	tag2	1	0	13.8.10	tag2	1	0	1	0
229	t1g3	1	1	20.9.10	0	0	0	0	0
230	t1g3	1	1	22.9.10	0	0	0	0	0
231	t1g3	1	1	8.6.10	0	0	0	0	0
232	tag2	0	0	5.8.10	0	1	0	0	0
233	tag2	0	0	3.1.11	0	0	0	0	0
234	tag2	0	0	16.7.10	0	0	0	0	0
235	tag2	1	0	6.4.10	0	0	0	0	0
236	tag2	1	0	8.4.10	0	0	0	0	0
237	tag2	0	0	8.4.10	0	0	0	0	0
238	tag2	0	0	8.4.10	0	0	0	0	0
239	t1g2	1	0	12.4.10	0	0	0	0	0
240	t1g2	1	0	14.4.10	0	0	0	0	0
241	t1g2	1	0	17.4.10	0	0	0	0	0
242	t1g3	1	1	27.4.10	0	0	0	0	0
243	t1g3	0	1	14.7.10	0	0	0	0	0
244	tag2	1	0	3.5.10	0	0	0	0	0
245	t1g2	1	1	16.8.10	0	0	0	0	0
246	t1g2	1	0	10.5.10	0	0	0	0	0
247	t1g3	0	1	13.5.10	0	0	0	0	0
248	t1g2	1	0	25.5.10	0	0	0	0	0
249	t1g3	1	1	17.1.11	0	0	0	0	0
250	t1g2	1	0	2.2.09	0	0	0	0	0